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VOLUME 5 *Boston Number* NUMBER 5

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MARCH, 1922

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THE MEDICAL CLINICS
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VOLUME 5 NUMBER 5

CONTRIBUTION BY DR. HENRY A. CHRISTIAN

PETER BENT BRIGHAM HOSPITAL

DIGITALIS EFFECTS IN CHRONIC CARDIAC CASES WITH REGULAR RHYTHM IN CONTRAST TO AURICULAR FIBRILLATION

IN 1919, in a paper entitled "Digitalis Therapy: Satisfactory Effects in Cardiac Cases with Regular Rhythm" (Amer. Jour. Med. Sci., 1919, clvii, 593), I ended with these words, "These cases may serve as examples of what we commonly observe in cardiac cases with arrhythmia, and justify placing much confidence in the effects of digitalis on cardiac patients with regular pulses. They certainly justify a confident use of digitalis in such cases, even though the pulse rate may not be rapid. Even when the pulse rate is not changed, other striking changes are produced, and the patient is benefited by digitalis therapy when it is properly administered."

Mackenzie (chapter on "Chronic Diseases of the Heart," Oxford Medicine, Vol. II) believes that digitalis has its chief effect on heart rate, particularly when there is arrhythmia. "They" (drugs of the digitalis group), says Mackenzie, "seem, however, to have a very restricted action, chiefly limited to the slowing of the heart's rate in certain abnormal rhythms of the heart. This is probably due to their action on some part of the regulating mechanism of the heart's rate chiefly, if not entirely, through the vagus. Whether these drugs have any action beyond slowing is doubtful, except it may be in their effect upon that somewhat mysterious function of the heart muscle—tone.

"*Digitalis.*—In an inquiry I have conducted for many years on the action of this drug, in every instance where I got a good result from its action on the heart, it was accompanied by a diminution of the heart's rate. . . . Apart from these cases in which improvement occurred with slowing of the rate, the only other condition I have found benefited by digitalis was in dropsy, when the digitalis acted as a diuretic.

"The best effect of digitalis is seen in cases of heart failure with dilatation of the heart and dropsy. Eighty or 90 per cent. of such cases suffer from auricular fibrillation. . . . If we scrutinize the published records of cases that have benefited by the drug, we find that the great majority of these results occur in one condition, auricular fibrillation, or its allied condition, auricular flutter. . . . Indeed, my experience has been that with normal rhythm only occasionally does the digitalis slow the heart, and that to a very slight degree" (Oxford Medicine, Vol. II, pp. 487 and 488).

My views evidently differ from those of my fellow editor of the Oxford Medicine. The views of Sir James Mackenzie, as outlined in the above quotations from him, have been concurred in by numerous observers, with the result that there is a growing feeling that, unless the pulse is absolutely irregular and rapid, little is to be gained from digitalis therapy. My own experience is so directly contrary to this that it seems worth while to restate the views already expressed by me in the quoted article and to support them with further data.

My own view with regard to digitalis is that digitalis, as a rule, has a striking effect on those changes in the patient which are brought about by cardiac insufficiency, and this effect appears irrespective of whether or not the pulse is irregular. The following changes are the prominent ones in patients suffering from cardiac insufficiency: increased heart rate with and without arrhythmia, dyspnea, cough, cyanosis, edema, decreased urine output, nausea, vomiting, enlargement of the liver, pain. Some or all of these are found in individual patients. Alteration of some or all of these is to be looked for following digitalis therapy as evidence of effectiveness of the drug. Some

only of these changes can be presented in a striking, graphic way. Some are rather apt to be overlooked because the appropriate observations are not made on the patients; moderate diuresis will not be noted unless the urine amount and the fluid intake for each twenty-four hours is recorded, and often loss of edema may be indicated graphically only by decline in the patient's weight, for the increase in urine output may be but slight, with a rapidly falling weight curve. Changes in heart rate, particularly if both apex and radial rates are charted, show in a striking way on the clinical chart. It is to be remembered that with arrhythmia pulse rate may be no index of heart rate; with arrhythmia it is essential to count the apex rate. Dyspnea is poorly, sometimes not at all, depicted by the charted rate of respiration. Evidence of decreased dyspnea, cough, and cyanosis has to be found in the daily notes made on the patient's condition. Decreases in edema are indicated graphically in the urine amount and actually depicted in the weight curve. Improved renal function is shown by an increased output and in improved figures for renal function. Nausea, vomiting, and pain conditions must be described. Shrinkage in liver size is to be noted in abdominal palpation. Improvement in the patient's general condition as well as in a number of these special symptoms is a matter of clinical observation rather than of graphic numerical record, but these are none the less important on that account.

If patients with cardiac disease are observed in these various ways, and if the observations are systematically recorded, it is the exception to fail to find definite evidence of a very considerable result from digitalis therapy provided signs of cardiac insufficiency were present prior to giving the digitalis, the digitalis used is potent and given in sufficient amount, and there has been a fair interval of time since any preceding digitalis therapy.

I often wonder if, perchance, the great reputation for efficiency of digitalis in auricular fibrillation does not depend in large part on the fact that the heart rate in these cases is often very rapid when the heart is decompensated and it is so easy to be impressed by its marked slowing, as shown on the

clinical chart, after digitalis has been given. True it is, that it is rare to see so marked a slowing from digitalis when cardiac rhythm is regular. This, however, is due to the fact that digitalis

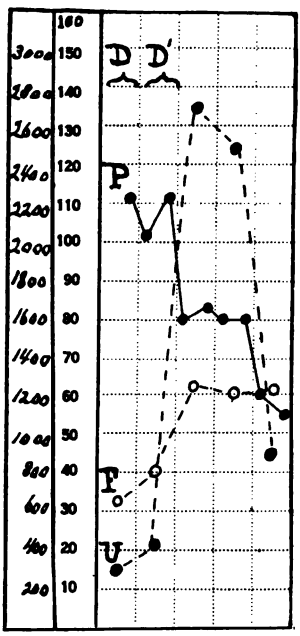

Fig. 226.—Male, age twenty-eight, chronic cardiac valvular disease, mitral stenosis; rhythm regular. The first column of figures on the left-hand side of the chart indicates the amount of urine output and the fluid intake for each twenty-four hours expressed in cubic centimeters. The second column of figures on the left of the chart indicates the apex and radial pulse rates per minute. D = three doses of 0.2 gm. each of powdered digitalis leaves every six hours, a total of 0.6 gm. on this day. D^1 = seven doses of 0.3 gm. each of powdered digitalis leaves every six hours, a total of 2.1 gm. on this day. Total D + D^1 = 2.7 gm. of powdered digitalis leaves. P = pulse rate counted at the wrist. F = fluid intake measured in cubic centimeters. U = urine measured in cubic centimeters. The effect of digitalis in this case was a slowed pulse (110 to 55) and on two days a marked diuresis, with urine increase from 400 to 2700 and 2500 c.c.

in therapeutic doses, as a rule, slows the rate to but 60 to 70, and if before its use the rate was 90 to 110, as is usually the case in decompensation with regular rhythm, the decrease is not a very striking thing (Fig. 226), while if the rate beforehand

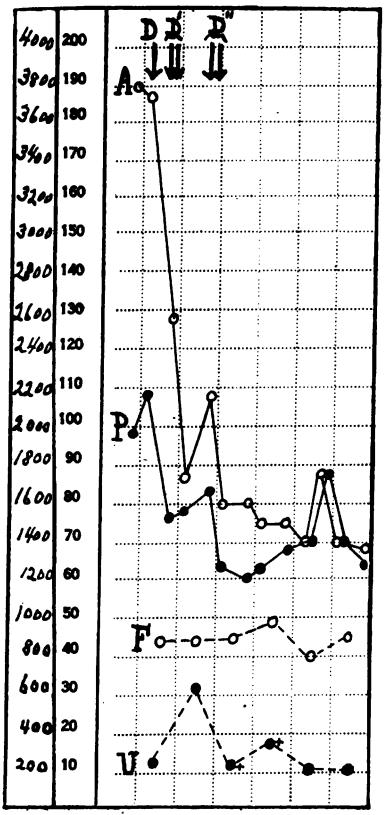

Fig. 227.—Female, age twenty-eight, chronic cardiac valvular disease, mitral stenosis and regurgitation, aortic regurgitation; auricular fibrillation. The first column of figures on the left-hand side of the chart indicates the amount of urine output and the fluid intake for each twenty-four hours expressed in cubic centimeters. The second column of figures on the left of the chart indicates the apex and radial pulse rates per minute. D = 1 c.c. tincture of digitalis given intravenously at 10.12 A. M. D^1 = two doses of 0.5 gm. of powdered digitalis leaves given at 1.52 and 8 P. M., a total of 1 gm. D^2 = two doses of 0.1 gm. of powdered digitalis leaves given at 6 and 10 P. M., a total of 0.2 gm. Total D + D^1 + D^2 = 1 c.c. of tincture intravenously and 1.2 gm. of powdered digitalis leaves by mouth. A = heart rate counted with a stethoscope over the apex region. P = pulse rate counted at the wrist. F = fluid intake measured in cubic centimeters. U = urine measured in cubic centimeters. The effect of digitalis in this case was a slowed apex rate (190 to 70), with disappearance of pulse deficit.

was 160 or more, as occurs in auricular fibrillation, the curve on the clinical chart rightly may be termed a "dramatic change" (Fig. 227).

However, these very rapid heart rates are not so very frequent in auricular fibrillation; in our series only 3 patients

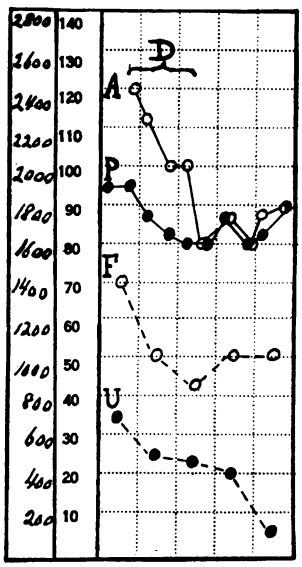

Fig. 228.—Female, age eighteen, chronic cardiac valvular disease, mitral stenosis and insufficiency; auricular fibrillation. The first column of figures on the left-hand side of the chart indicates the amount of urine output and the fluid intake for each twenty-four hours expressed in cubic centimeters. The second column of figures on the left of the chart indicates the apex and radial pulse rates per minute. D = seven doses of 0.1 gm. each of powdered digitalis leaves every six hours, a total of 0.7 gm. A = heart rate counted with a stethoscope over the apex region. P = pulse rate counted at the wrist. F = fluid intake measured in cubic centimeters. U = urine measured in cubic centimeters. The effect of digitalis in this case was a slowed apex rate (120 to 80), with disappearance of pulse deficit.

among 57 with auricular fibrillation had an apex rate over 140 at the time digitalis was given. Sixteen had an apex rate under 90, 9 a rate of 90 to 100, 7 a rate of 105 to 110, 6 a rate of 115 to 120, 10 a rate of 125 to 130, 6 a rate of 135 to 140. Consequently a heart rate of 115 to 120 may be said to be fairly typical

of auricular fibrillation, and at such a level the effect of digitalis on pulse rate (Fig. 228) is not very different from that in the faster heart rates of patients with regular rhythm (compare with Fig. 226). In contrast to these patients with auricular fibrillation, of 40 patients with regular rhythm, 16 had a heart rate under 90, 13 a rate of 90 to 100, 3 a rate of 105 to 110, 6 a rate of 115 to 120, 2 a rate of 125 to 130, and none faster. Hence, a rate of 95 to 100 may be said to be an average for cases with regular rhythm. Often I have seen these slower rates, however, show other changes in conditions fully as "dramatic" as the slowing of the fast pulse of auricular fibrillation; as, for example, Fig. 229, showing diuresis and drop in body weight.

For some years in my clinic at the Peter Bent Brigham Hospital all patients have had the daily fluid intake and urine output measured and charted. All patients are weighed at frequent intervals. All patients with irregular cardiac rhythms have the cardiac rate counted with the stethoscope on the apex region and the pulse counted at the wrist, and these are charted. With few exceptions cardiac cases have electrocardiograms made. The clinical chart shows the amount of digitalis given each day, so that digitalis therapy appears on the chart in relation to temperature, pulse and apex rate, rate of respiration, fluid intake, urine output, and patient's weight. This makes it relatively easy to note digitalis effects. To check up my impressions I have reviewed the records of 97 consecutive patients with some form of chronic cardiac disease in relation to digitalis effectiveness. With rare exceptions all such patients have had digitalis therapy in moderate to large dosage. Of these 97 patients, 72, or 74.2 per cent., show in their records definite and considerable change following digitalis therapy; 8, or 8.2 per cent., show definite though slight digitalis effect, while only 17, or 17.5 per cent., give no evidence that digitalis has produced any change.

In this study a decrease in heart rate of not less than 30 beats per minute, a loss in body weight of at least 4 kilos (8.8 pounds), or a diuresis with urine output either for a day much

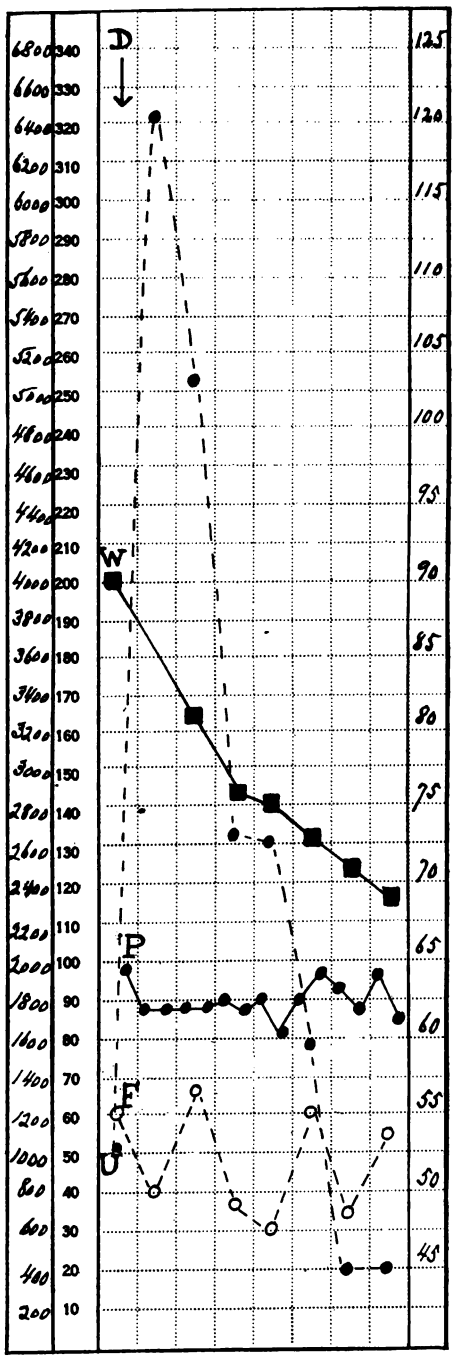

Fig. 229. (For legend see next page.)

in excess of fluid intake or for several days considerably in excess of fluid intake, provided these changes followed digitalis therapy, were considered sufficient evidence of definite and considerable effect of digitalis. If these changes were not shown in the chart the patient's record was read particularly for evidence of other changes; in one patient a marked decrease in liver size and in another a marked improvement in dyspnea were accepted as evidence of definite and considerable digitalis effect. With these two exceptions all of the cases showed at least as much change as indicated by the criteria set for pulse, body weight, or urine output change. Obviously very many patients showed much more change than these minima, and usually a number of symptoms and signs were very definitely improved by the digitalis.

With extremely rare exceptions (intravenous strophanthin) no other drug of the cardiac group other than digitalis is used at the Peter Bent Brigham Hospital, and in almost every case the same preparation, namely, pills of powdered leaves, is employed; very occasionally other forms of digitalis are used. Fluid intake is restricted in most of these cases as shown by the charts. Very cyanotic patients are bled. Copious catharsis is not employed. Morphin is used for restless patients. Patients are in bed, for the most part propped on a bed-rest. Digitalis is the sheet anchor in treatment. It is certain that essentially the same treatment is followed for patients with regular and with irregular heart rhythms. Consequently, results are com-

Fig. 229.—Male, age forty-five, chronic myocarditis, hypertension, rhythm regular. The first column of figures on the left-hand side of the chart indicates the amount of urine output and the fluid intake for each twenty-four hours expressed in cubic centimeters. The second column of figures on the left of the chart indicates the apex and radial pulse rates per minute. The column of figures on the right indicates the weight of the patient in kilograms. D = a single dose of 2.3 gm. of powdered digitalis leaves given at 10.30 A. M. P = pulse rate counted at the wrist. F = fluid intake measured in cubic centimeters. U = urine measured in cubic centimeters. W = weight of the patient in kilograms. The effect of digitalis in this case was to produce a very marked diuresis with increase of urine from 1000 to 6425, 5050, 2625, and 2600 c.c., and a decrease in body weight of 21.4 kilos, or 47 pounds.

parable in these two groups. Treatment other than giving digitalis is, of course, important, but it is not sufficient to produce the results attributed to the digitalis, as has been shown in numerous patients in whom these other procedures were instituted, and digitalis then given after four or five days of the other management.

Figures for the Peter Bent Brigham Hospital clinic are, with rhythms regular (except, at most, for occasional extrasystoles or delayed conduction time), 40 cases, of which 5 were diagnosed mitral stenosis and insufficiency; 1 aortic stenosis; 5 aortic regurgitation; 6 aortic regurgitation and mitral stenosis; and 23 chronic myocarditis. With auricular fibrillation[1] there were 57 cases, of which 13 were diagnosed mitral stenosis and insufficiency; 4 aortic regurgitation and mitral stenosis, and 40 chronic myocarditis.

	Per cent
With regular rhythm considerable digitalis effect in	72.5
With auricular fibrillation considerable digitalis effect in	75.4
With regular rhythm slight digitalis effect in	5.0
With auricular fibrillation slight digitalis effect in	10.5
With regular rhythm no digitalis effect in	22.5
With auricular fibrillation no digitalis effect in	14.0

The diagnosis of cardiac rhythm in all cases used in the above tabulation is based on electrocardiographic study.

This tabulation shows that digitalis produces a considerable change with almost equal frequency whether auricular fibrillation is present or not. The striking thing is that, with so very few exceptions, evidence of definite, considerable digitalis action is present. If we examine these cases further we find that usually where digitalis effect is slight or absent (25 of 97 cases) it is because patients really had no definite evidence of cardiac decompensation (16 cases); less often the cause was found in the fact that the patient was too near death for the drug to act (6 cases). Here, however, it is remarkable that definite effects sometimes may be obtained in patients who

[1] In this series there was only one case with auricular flutter, and for simplicity this is omitted from the tabulation.

actually die within four or five days after the digitalis effect is obtained.

As already quoted, Mackenzie in his experience found that whenever he got a good result from the action of digitalis on the heart, it was accompanied by a diminution of the heart's

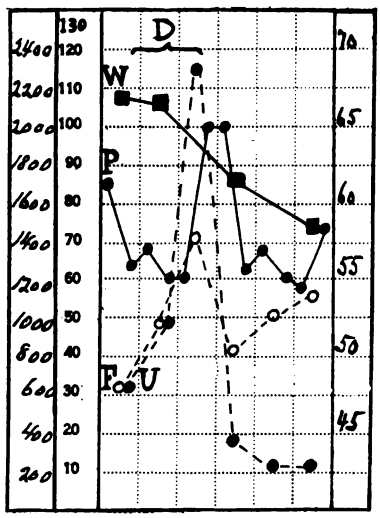

Fig. 230.—Male, age sixty, chronic myocarditis, rhythm regular. The first column of figures on the left-hand side of the chart indicates the amount of urine output and the fluid intake for each twenty-four hours expressed in cubic centimeters. The second column of figures on the left of the chart indicates the apex and radial pulse rates per minute. The column of figures on the right indicates the weight of the patient in kilograms. D = eight doses of 0.2 gm. each of powdered digitalis leaves every six hours, a total of 1.6 gm. P = pulse rate counted at the wrist. F = fluid intake measured in cubic centimeters. U = urine measured in cubic centimeters. W = weight of the patient in kilograms. The effect of digitalis in this case was a moderately slowed pulse-rate (85 to 60), a diuresis with urine increase from 625 to 975 and 2300 c.c., and a decrease in body weight of 7.8 kilos, or 17.2 pounds.

rate. Since increased cardiac rate is one of the commonest evidences of cardiac insufficiency, obviously it will be found in the great majority of patients to whom digitalis is given, for all agree that digitalis therapy is indicated only when there is evidence of cardiac insufficiency. If increased cardiac rate

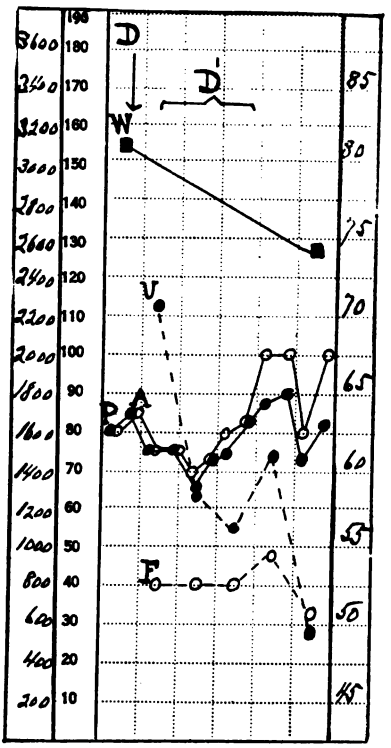

Fig. 231.—Female, age forty-five, chronic myocarditis, auricular fibrillation. The first column of figures on the left-hand side of the chart indicates the amount of urine output and the fluid intake for each twenty-four hours expressed in cubic centimeters. The second column of figures on the left of the chart indicates the apex and radial pulse rates per minute. The column of figures on the right indicates the weight of the patient in kilograms. D = 0.5 gm. of powdered digitalis leaves given at 3.35 P. M. D^1 = nine doses of 0.2 gm. each of powdered digitalis leaves given four times a day, a total of 1.8 gm. Total D + D^1 = 2.3 gm. of powdered digitalis leaves. A = heart rate counted with a stethoscope over the apex region. P = pulse rate counted at the wrist. F = fluid intake measured in cubic centimeters. U = urine measured in cubic centimeters. W = weight of the patient in kilograms. The effect of digitalis in this case was a diuresis with urine output of 2250 c.c. and a decrease in body weight of 7 kilos, or 15.4 pounds.

is present in cardiac insufficiency prior to digitalis therapy and the therapy is effective, it is to be supposed that the rate will be slowed. This is the case except in those patients in

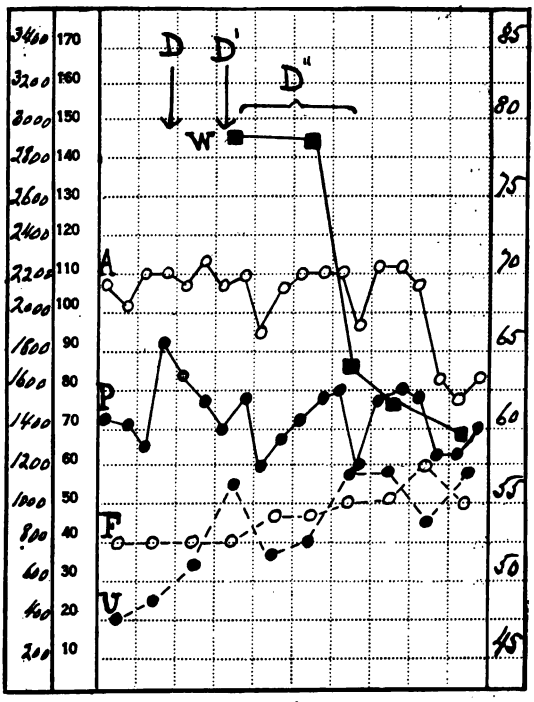

Fig. 232.—Male, age fifty-nine, chronic myocarditis, auricular fibrillation, arteriosclerosis, old right hemiplegia. The first column of figures on the left-hand side of the chart indicates the amount of urine output and the fluid intake for each twenty-four hours expressed in cubic centimeters. The second column of figures on the left of the chart indicates the apex and radial pulse rates per minute. The column of figures on the right indicates the weight of the patient in kilograms. D = a single dose of 1.8 gm. of powdered digitalis leaves. D^1 = 0.2 gm. of powdered digitalis leaves. D^2 = fifteen doses of 0.1 gm. each of powdered digitalis leaves every six hours, a total of 1.5 gm. Total D + D^1 + D^2 = 3.5 gm. of powdered digitalis leaves. A = heart rate counted with a stethoscope over the apex region. P = pulse rate counted at the wrist. F = fluid intake measured in cubic centimeters. U = urine measured in cubic centimeters. W = weight of the patient in kilograms. The effect of digitalis in this case was a delayed decrease in apex rate (110 to 78), with a moderate decrease in pulse deficit, a delayed but prolonged moderate diuresis, and a decrease in body weight of 19 kilos, or 41.8 pounds.

which the increased rate is due to a paroxysmal tachycardia or paroxysmal auricular fibrillation associated with cardiac insufficiency. Here the rate may be irrespective of digitalis

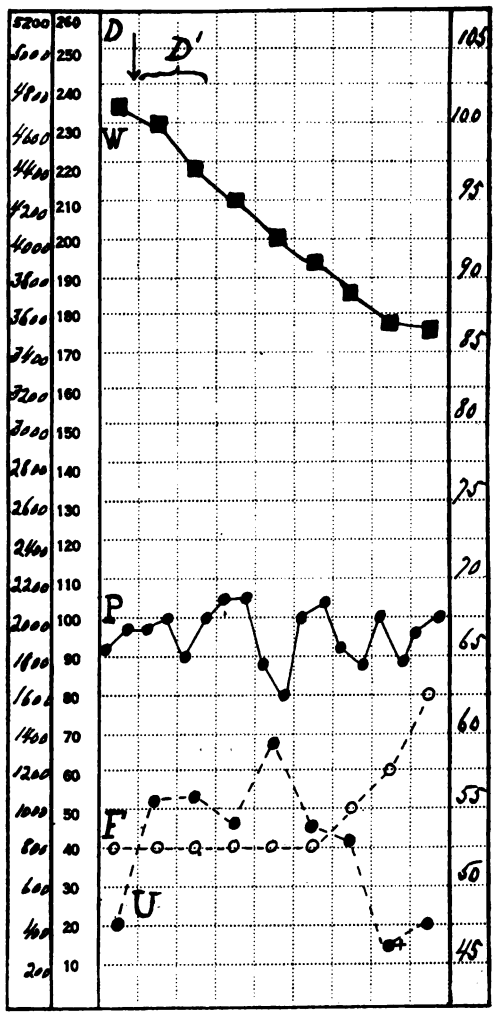

Fig. 233.—Female, age forty-three, chronic myocarditis, hypertension, rhythm regular. The first column of figures on the left-hand side of the chart indicates the amount of urine output and the fluid intake for each twenty-four hours expressed in cubic centimeters. The second column of figures on the left of the chart indicates the apex and radial pulse rates per minute. The column of figures on the right indicates the weight of the patient in kilograms. D = a single dose of 1.2 gm. of powdered digitalis leaves given at 9.30 P. M. D^1 = five doses of 0.2 gm. each of powdered digitalis leaves every six hours, started at 3.30 A. M., a total of 1 gm. Total D + D^1 =

therapy, a period of rapid rate starting and ending abruptly, as it does, without any relation to digitalis. Another exception lies in those cases in which the increased rate is part of a febrile condition. Here digitalis has little effect on rate. However, there are cases in which the heart is decompensated and yet the rate is slow. In these there may be very striking digitalis effects, and they occur with both regular rhythm and auricular fibrillation, as shown by the following examples (Figs. 230, 231). These are cases with dropsy and the striking effect is diuresis, a possibility recognized by Mackenzie in the words, "the only other condition I have found benefited by digitalis was in dropsy, when the digitalis acted as a diuretic." However, weight decrease with slight diuresis may be a result of digitalis therapy as shown by the following cases (Figs. 232, 233), and if diuresis alone is taken as the criterion of an effect of digitalis on edema, some striking effects such as these may be overlooked.

An enlarged liver may decrease in size with disappearance of tenderness as a result of digitalis without there being either decreased pulse rate or diuresis, as shown by the following case (Fig. 234). The same thing may happen with regard to dyspnea and with other symptoms of cardiac insufficiency, changes which cannot be presented in any graphic way, but which depend on words expressive of judgments and opinions from day to day. These are no less real, but as they have no numerical measurements they are more open to the bias of the personal equation, and hence not so well suited to such a study as the present. However, these other changes, which may be expressed objectively and numerically, are encountered so often in cardiac patients following digitalis therapy that we may rest the case on them, and say that in a very large percentage of all cardiac cases with insufficiency digitalis produces definite objective changes which may be expressed numerically, and this is true

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2.2 gm. of powdered digitalis leaves. P = pulse rate counted at the wrist. F = fluid intake measured in cubic centimeters. U = urine measured in cubic centimeters. W = weight of the patient in kilograms. The effect of digitalis in this case was a slight prolonged diuresis and a decrease in body weight of 15 kilos, or 33 pounds.

with little variation dependent on regular or irregular rhythm. In other words, digitalis is fully as efficient with regular rhythm as with auricular fibrillation. The change produced in auricular fibrillation may be more readily noted, but often it is not a

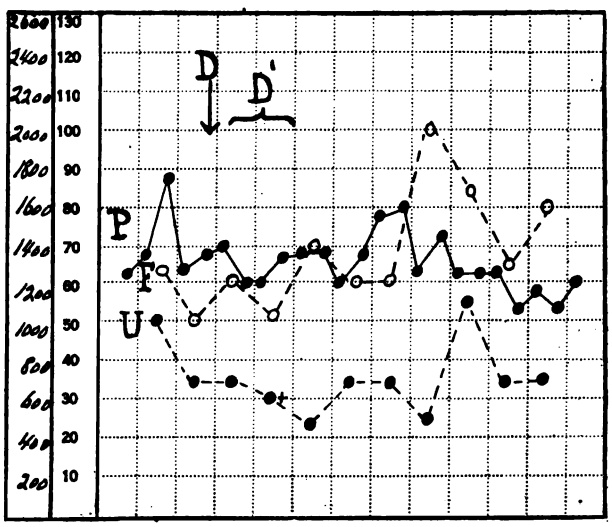

Fig. 234.—Female, age fifty-seven, chronic cardiac valvular disease, aortic and mitral insufficiency, rhythm regular. The first column of figures on the left-hand side of the chart indicates the amount of urine output and the fluid intake for each twenty-four hours expressed in cubic centimeters. The second column of figures on the left of the chart indicates the apex and radial pulse rates per minute. D = a single dose of 0.2 gm. of powdered digitalis leaves, given at 5 P. M. D^1 = six doses of 0.2 gm. of each of powdered digitalis leaves given three times a day, beginning at 10 A. M., a total of 1.2 gm. Total D + D^1 = 1.4 gm. of powdered digitalis leaves. P = pulse-rate counted at the wrist. F = fluid intake measured in cubic centimeters. U = urine measured in cubic centimeters. The effect of digitalis in this case was a marked decrease in size of the liver without change in pulse-rate or urine output.

whit more dramatic than changes found in cardiac patients with regular rhythm, and by and large digitalis is just as efficient a therapeutic agent in chronic cardiac lesions with insufficiency whether there is auricular fibrillation or regular rhythm. Certainly there is no reason to believe, prior to trial,

that digitalis is unlikely to be an effective therapeutic agent because the auricles are not fibrillating.

If there is marked evidence in the patient of cardiac decompensation, as indicated by such signs as rapid heart rate, dyspnea, cyanosis, edema, etc., digitalis, if potent and given in adequate dosage, with few exceptions, produces very evident changes. This is shown by the experience just cited where among 97 unselected cases such a digitalis effect was obtained in 72 (74.2 per cent.) of the patients. Of the 25 not showing a considerable digitalis effect the failure was due in 16 cases to the fact that there were present but very slight signs and symptoms indicating cardiac insufficiency, and so giving digitalis could hardly be expected to make much change; in these cases it was given more as a therapeutic test to see if any improvement would come than from a belief that it was strongly indicated as a therapeutic measure. In 6 more of the 25 cases the patients died so soon that it is not surprising that the heart failed to respond to digitalis. Of the remaining 3, 1 with slow pulse and edema had evident nephritis, which seemed to be the cause for digitalis not producing a diuresis, 1 had an aortic aneurysm which was in part responsible for symptoms, and in 1 there seemed no reason why a digitalis effect was not produced, possibly the drug was not absorbed. Omitting the 16 cases with slight signs of cardiac decompensation, 81 remain in which there were evident signs of cardiac decompensation, and of these, all but 9 showed definite, considerable digitalis effect, *i. e.*, 90 per cent. showed definite, considerable digitalis effect. Of the 9 failures the cause for 6 was found in impending death, for 1 in chronic nephritis preventing diuresis, and for 1 in an aortic aneurysm, leaving but 1 failure, for which there seemed no adequate cause. That auricular fibrillation plays but little part in determining digitalis effectiveness is shown by the results, adequate digitalis effect in 72.5 per cent. of the cases with regular rhythm in contrast to 75 per cent. of the cases with auricular fibrillation.

Conclusion.—Digitalis is fully as effective in the treatment of chronic cardiac cases without auricular fibrillation as it is

in those with auricular fibrillation. Even when the heart rate is slow striking digitalis effects may be produced whether fibrillation is present or not. If symptoms and signs of cardiac decompensation are marked it is rare to fail to get a digitalis effect irrespective of what the cardiac rhythm is.

CLINIC OF DR. WILLIAM H. ROBEY

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ANGINA PECTORIS WITH AND WITHOUT CARDIAC SIGNS

So much has already been said and written about angina pectoris that it should be familiar to all physicians; yet our knowledge of the condition is somewhat fragmentary. When we use the term *angina pectoris* we are, of course, referring to a symptom which broadly includes all forms of precordial pain, whether due to coronary disease, aortic regurgitation, mitral stenosis, excessive use of tobacco, simple indigestion, or some of the nervous manifestations involving the heart, such as effort syndrome. Many people are alarmed by the presence of pain in the precordial or adjacent areas, and seek advice for this symptom alone, and it is only by thorough study of the history and the subjective and objective symptoms that the physician can assure himself of its importance or unimportance.

CAUSES AND DISTRIBUTION OF PAIN

Young persons have pain about the heart not infrequently when there is no evidence of cardiac disease, and the symptom often can be removed by a correction of the habits of eating. If the young person has evidence of aortic regurgitation, then the pain is probably due to sudden stretching of the aorta. This pain is usually high up under the sternum and often radiates to the shoulder. I have recently seen a young man of twenty-three and a girl of eighteen who illustrate this form of precordial pain. In both the aortic regurgitation was a result of rheumatic infection. In mitral stenosis, on the other hand, the pain is often about the area of the cardiac impulse. Know-

ing that pain occurs in the heart in both of these conditions and finding the physical signs of either aortic regurgitation or of mitral stenosis, the diagnosis is quite clear, and the treatment that which is ordinarily used in disease of those valves. Mackenzie believes that the pain in these conditions may be due to sudden stretching of the walls of the ventricles, or to the stretching of small portions of the walls of the ventricles.

In syphilitic aortitis the pain is often high in the chest, beneath the sternum, and may radiate to the shoulder, the inner side of the left arm, and sometimes to the fingers. We know that syphilitic aortitis may exist without involvement of the coronary artery, but it is difficult in dealing with this condition to disregard possible coronary disease, knowing as we do that while the arterial system may be sclerosed unequally, the entire system is affected in varying degrees.

During the war we saw many soldiers with precordial pain in neurocirculatory asthenia (effort syndrome)—a condition giving several heart signs without evident cardiac disease. Here, as in other forms of precordial pain without organic origin, the cause is quite obscure.

In simple indigestion in young persons, while the cause of pain is difficult to understand, a correction in the diet and attention to the bowels often stops the symptom.

In tobacco angina we have pain about the heart, sometimes quite indistinguishable from the pains of coronary disease; but if tobacco is given up the precordial discomfort will usually disappear in three or four weeks. Just why tobacco produces precordial pain is not understood; possibly the idea expressed by Pardee may be tenable: that tobacco produces pain by acting upon an already formed basis of disease that is not sufficiently marked to produce symptoms by itself alone.

DIAGNOSIS

The diagnosis in a young person may be open to considerable doubt, but if there is no evidence of cardiac or circulatory disease, no history suggesting the possibility of the formation of cardiac changes, no limitation in reserve force, then it is probable

that errors in diet and mode of living may be responsible for the discomfort, and attention to these factors will often quiet down the symptoms. There are patients who have pain about the heart at intervals for many years without any evident signs of cardiac or circulatory disturbance. Furthermore, they do not suffer from fatigue on exertion or from breathlessness. The pain may be sharp and sudden, a dull ache, or a pricking sensation about the nipple. Sometimes there is an area of hypersensitiveness in the precordium, as described by Mackenzie; sometimes an occasional premature contraction. In some of these cases a correction of diet or cessation of tobacco will stop the discomfort.

In the presence of aortic regurgitation the diagnosis is important, because with pain, especially in the syphilitic form of angina pectoris, it is an unfavorable symptom and sudden death may occur.

In mitral stenosis the pain is usually situated about the cardiac impulse and is not an ominous sign.

Some patients, after having vague symptoms occurring at long intervals for years, may develop a true angina, but it seems difficult to connect an occasional substernal pain in an apparently healthy individual with a fatal angina pectoris occurring many years later.

In 1768 Heberden gave the name of angina pectoris to this condition and attributed the pain to disease of the coronary arteries. Huchard considered that disease of the aorta was the cause, and Sir Clifford Allbutt has also upheld this view, but many physicians believe that occlusion of the branches of the coronaries is the cause of the pain and other symptoms.

While aortitis may exist without coronary disease, arterial disease does not select definite areas as a rule, and where it is due to infection or senile endarteritis the entire arterial system suffers in *varying degrees*. The recognition of a simple pericarditis would not be of such importance in itself were it not that in acute infections pericarditis, *myocarditis*, and endocarditis often go hand in hand.

In syphilitic aortitis when the patient comes under observa-

tion there is generally evident involvement of the arteries, although there are noticeable exceptions. The coronary artery frequently takes part in this process, so it is difficult to tell whether the pain is due to the aorta or the coronary, or to both.

Aortic regurgitation may give attacks of pain such as are described in angina pectoris, yet it is our experience that the majority of cases do not have the anginal type. On the other hand, one sees old persons in an initial attack of angina pectoris whose coronaries must have been undergoing degenerative changes for years. Even where there is no autopsy, we know that many branches have been gradually occluded until the cardiac muscle dies slowly from lack of nourishment or suddenly by occlusion of a large branch. In two patients, both of whom have lived long enough to have coronary sclerosis, why one has symptoms of angina pectoris and the other a slowly failing heart without the anguish of angina is difficult to understand. Osler has described three modes of dying in angina: First, the functions of life stop abruptly and, with a gasp, all is over. In the second form the patient dies in a state of progressive asthenia, the heart growing weaker after a series of attacks; and in the third, there is a gradually induced cardiac insufficiency with dyspnea.

Three types of angina pectoris have long been recognized: (1) The mildest form, existing for years, occurring often at long intervals, and disappearing entirely when certain habits have been removed or the patient has been relieved from strain and overwork. (2) The mild form, in which attacks more or less characteristic of angina exist for months or years, sometimes disappearing but tending to recur in more violent form, and often ending in sudden death. (3) The severe form, in which the attacks come on with great violence, often without any cause, such as overexertion or an indigestible meal, tending to steadily increase in severity and ending in sudden death.

In all of the excellent articles on this subject which appear in many of the text-books and also in recent monographs mention is made of the fact that *true angina pectoris may exist without any cardiac signs whatever*, and the chief object of the paper is

to emphasize this point, for the reason that some of our mistakes seem to come from the fact that because there are no evident signs of cardiac disease, we are inclined to disregard the presence of this important symptom. As I have already said, when the condition occurs in young people, without the history or evidence of cardiac disease, we are often justified in disregarding pain about the heart; but when it occurs in middle-aged or old people, *especially if it has the characteristics of true angina pectoris, it should never be disregarded.* A good deal has been written about the character of the pain in true angina pectoris, and much has been said about its localization; but it seems to me that the most important form of angina pectoris, which is due to coronary disease, has, as a rule, characteristics which are quite unlike any other form of precordial pain.

Many of the middle-aged individuals who seek advice because of these symptoms attribute their discomfort to indigestion because the attacks of angina are often accompanied by flatulence and a sensation of gastric distress; and we have all seen cases of coronary disease which have been diagnosed as indigestion and unsuccessfully treated as such. It is not uncommon to see in the newspapers an account of the death of an elderly prominent citizen who was seized with an attack of acute indigestion resulting fatally within an hour or two of its onset. This is almost invariably the result of coronary disease. In precordial pain due to coronary disease the attacks often come on immediately after undue exertion, but a very striking fact is that they *frequently occur at night* after the patient has been asleep a few hours, and sometimes when he is sitting quietly.

My experience differs from Pardee's, since I have found that the pain is often high up in the chest, under the clavicles; and very often there is a sense of constriction rather than pain; often there is a feeling as if the neck was being squeezed, and this sensation in some instances gives the patient with true angina pectoris more discomfort than the pain. When the true attack is over the patient feels exhausted, and many times has a profuse sweat.

An example of the type of case of angina pectoris which may

exist without any symptoms whatever referable to the heart is illustrated in the following history:

A man forty-seven years of age, whose father had died at the age of seventy-one of angina pectoris, gave a history of freedom from serious infections and was not aware of having contracted any venereal disease. Five years before I saw him he had a pain in the chest radiating to both arms. This condition repeated itself several times and was followed by a year and a half of complete freedom. Five months before I saw him the attacks began again following exertion of any kind, and frequently came on in the early morning after a satisfactory sleep. He had used alcohol moderately and smoked fifteen cigarettes a day. His appetite was extremely good. There was no nocturia. The attacks of pain were intense, located underneath the sternum and radiating to the shoulders, back, and arms. The attack would last sometimes for half an hour, at the end of which time the patient was utterly exhausted and covered with profuse perspiration. He had seen a number of physicians: first, a gastro-enterologist, who had put him through all of the gastro-intestinal tests, with negative findings. He was then under the care of a neurologist for several weeks, who treated him for a neuritis of the left arm. At the time I saw him the physical examination was quite negative. There were no abnormal sounds in the heart. The aortic second was not accentuated, the blood-pressure was normal, the radial was not atheromatous. The *x*-ray plates of the heart showed that the heart and great vessels were normal. The Wassermann test was negative. An electrocardiogram showed an inverted T wave in Leads 2 and 3. The patient was kept in bed at complete rest, and was given antiluetic treatment notwithstanding his negative Wassermann, and sedatives in proper quantities to relieve pain. In spite of this, he continued to have attacks and died suddenly one month later. It is evident because of the almost complete negative findings in the heart and blood-vessels that this patient's condition had existed for several years without diagnosis, and was attributed to the stomach and nerves, but never to coronary disease.

The next case illustrates the difficulty of diagnosis in an old person in apparently excellent physical condition. He was first seen August 5, 1920:

A man seventy-two years of age, who had led a very active life, at times living in mining-camps and riding miles in the saddle every day. His habits were excellent. Past history was good except for pneumonia when a young man, and what he described as "gall-bladder attacks" many years before. He came to see me because he had been having considerable gas and indigestion and felt nervous and irritable. He had consulted a physician, who had treated him for several weeks for indigestion. On examination it was found that the blood-pressure was 160/120; heart, normal area with clear sounds and only moderate accentuation of the aortic second. The pulse was 92 at the first examination, and the radial was only slightly sclerosed. There was an occasional premature contraction. The liver could be felt just below the costal margin and was slightly tender on pressure. With almost complete rest for three weeks, a light and easily digested diet, and small doses of digitalis the attacks of angina ceased. The blood-pressure fell to 130/80, the pulse to 72; and notwithstanding the lowered rate, the premature contractions became much less frequent. The patient continued to be perfectly comfortable, and felt so well that he begged me to allow him to make a trip to New Mexico, where he had some mining interests. On November 12th he reported that notwithstanding his generally improved condition, he had had two attacks of angina pectoris. The first was brought on by attending the funeral services of a Civil War comrade at which the patient acted as chaplain. He had a seizure and had to be carried out and taken home. About ten days later he had an altercation with a man on his place, and that produced a severe attack. In the intervals, however, he felt as well as ever. On November 20th he unduly exerted himself, was seized with a violent attack, and died before a doctor could reach him.

Another case illustrates the fact that coronary sclerosis must have been going on for years without giving any distressing signs:

A retired merchant of seventy-eight years, who had been slowing down for two or three years, gradually losing in weight, but able to be about and enjoy life, with good appetite and digestion and sleeping well, was seized at 6 o'clock in the evening with severe pain in the chest, never having had symptoms of this character before. The pain was accompanied by nausea and repeated vomiting. The pain radiated to the shoulders, the arms, the neck, and along the spine. The blood-pressure was 120/80, pulse 76, slightly irregular, of fair strength. There was a blowing murmur over the cardiac impulse, systolic in time, which had existed for twenty-five years. The heart was normal in size. Under complete rest in bed and morphin all the patient's symptoms gradually subsided, and in forty-eight hours he was quite comfortable and anxious to get up. Three days after the beginning of his attack he died suddenly, without warning.

Yesterday I saw a patient of sixty-two, but looking ten years younger, who has had attacks of substernal pain localized pretty definitely at the third space and radiating to the arms and fingers; a man of good habits, without history of venereal disease and with a negative Wassermann. The pain was first noticed three years ago after climbing a small hill, and occurred at intervals following exertion for some months. It then disappeared for a year and a half, and during this time the patient felt as well as ever. It occurred again a year ago, after he had carried a piece of furniture upstairs. The pain disappeared, but in the last two months it has been more or less evident after walking or going upstairs. Recently it has occurred several times *just after going to bed*. He has been seen twice by a competent physician, who, not finding any evidence of cardiac disease, has told him the pain is of no consequence. The physical examination of this patient is essentially negative, Wassermann negative, blood-pressure 140/100. Heart is normal in size by percussion and the fluoroscope; the great vessels are normal; pulse 76; no arrhythmia, no palpable atheroma. A soft blowing murmur was heard over the aortic space which we commonly associate with aortic sclerosis. In the *x*-ray plates

at about the third space on each side of the sternum and in the area where the patient complains of pain is an irregular hazy shadow which does not seem to be connected with the heart or great vessels, and which raises the question of the presence of a neoplasm. In view, however, of the rather long history of the case, the splendid general condition, and the lack of physical signs which one would expect to accompany a mediastinal growth, it would seem that such a diagnosis is unlikely. My belief is that this represents the pain of an early coronary sclerosis, and if the patient is careful about exertion I think his attacks may quiet down completely. There is always, however, in such a case the possibility of sudden death, as most of us know by experience.

The next 2 cases will illustrate, first, the gradual progress of coronary sclerosis with angina pectoris, and, the second, the rapid progression of the signs of this disease.

The patient, a man of sixty-five, active in an important business, was seen by me seven years before, with pain high in the chest and a sense of constriction following exertion. He was in the habit of walking from his house to his office, but, as time went on, after going a mile it would become necessary to take a carriage. The blood-pressure was often as high as 220/120. The arteries were more or less atheromatous, the aortic second loudly accentuated, the size of the heart slightly increased. There was nocturia. At times there were attacks of flatulent indigestion, occasionally accompanied by vertigo and vomiting. This patient lived for seven years after he was first seen, during which time the attacks of angina pectoris became more frequent, more severe, and were often followed by exhaustion and sweating; the reserve force of the heart became greatly diminished, so that toward the end the patient was confined to bed without, however, any of the signs of stasis. During the last few weeks the attacks were very severe, the pain lasting often for an hour or two; and finally death occurred, not with the usual suddenness described in some of the other cases, but gradually sinking into an asthenic state.

The next case illustrates a rather rapid development with

changing heart signs: A manufacturer, fifty years old, married, had always been well until six months before he was seen by the writer, on April 28, 1921. He had never had rheumatism or syphilis, and his Wassermann was negative. During the week previous to his first visit, on three successive mornings, he had a feeling of constriction in the chest, starting in the left arm, passing up to the shoulders and the right arm. There was no palpitation and no attacks had occurred in the night. The heart was normal in size. There were no murmurs and no findings about the aorta to suggest atheroma or aneurysm. An *x*-ray plate at this time showed a normal heart and blood-vessels. Some of his attacks followed eating, others ordinary exertion, such as walking or going upstairs. Gradually, in spite of complete rest in bed with cardiac tonics, the seizures continued to increase in frequency and intensity. They occurred at various times in the day, and particularly at night and in the early morning. I saw him in two attacks, and both had the appearance of true angina pectoris such as I have been attempting to describe. The pain occurred high in the chest and about the clavicles, was sharp and agonizing. There was a sensation of constriction in the chest, and especially at the root of the neck. The man was pale and his face was covered with perspiration. A few whiffs of amyl nitrite and the attack quickly subsided. Sodium nitrite seems to produce very little effect on the attacks, but they were almost always subdued by amyl nitrite. In spite of the best care the attacks continued in severity, the heart gradually enlarged, a blowing systolic murmur was heard at the apex, the heart sounds were of poor quality, and the rate gradually increased. This patient died suddenly in the night, and was found holding a pearl of amyl nitrite which he had evidently attempted to inhale.

The point which I wish to emphasize is that coronary sclerosis is often quite free from cardiac signs, but in middle-aged and elderly people the presence of precordial pain, even in the absence of cardiac signs, especially when this pain is of the character which I have mentioned, should always be regarded as a very important and serious sign. If the heart shows any

form of irregularity, such as premature contractions, auricular fibrillation, or heart-block, we are not, as a rule, left in doubt as to the important meaning of angina pectoris, because we know that the presence of these irregularities almost always means fibrosis of the cardiac muscle or *lack of nutrition.*

Thomas Lewis observed that ligation of a coronary artery was followed quickly by single extrasystoles arising in one ventricle or the other. Within one to one and a half hours there occurred rapid successions of ventricular extrasystoles, producing attacks of ventricular tachycardia at rates of 300 to 420 per minute. In some instances the ventricles went into fibrillation and the dogs died. F. M. Smith confirmed the work of Lewis and continued to study the surviving dogs, describing a definite series of changes in the T wave which he considered characteristic effects of coronary occlusion. Lewis states that unexpected death may follow embolism or other obstruction of the coronary artery—a fact that has long been recognized; experiment indicates that fibrillation of the ventricle is the important cause of these catastrophes.

Pardee calls attention to the fact that the systolic blood-pressure and especially the pulse pressure are found to be abnormally low during the attack, and that these increase as the patient recovers, and will remain depressed for a longer time after the more severe attacks. This is a point which we all have had the opportunity to observe when we have been fortunate enough to see a patient during an attack.

The pericardial friction-rub which writers on this subject have recently referred to may be heard in cases where there is no attack of angina pectoris. In the hospital we see from time to time patients suffering from renal disease and arteriosclerosis, who in the course of a routine examination show transient pericardial rubs. These are probably due to small infarcts in the wall of the myocardium produced by the thrombosis of a fine branch of the coronary.

I do not think that at the present time any material help is to be obtained from electrocardiograms in these cases. Willius, in his book on *Clinical Electrocardiography*, reports electro-

cardiographic studies in 155 cases of angina pectoris, in 11.6 per cent. of which are found alterations in the T wave. In electrocardiographic studies in 9 of Longscope's cases that were proved at autopsy to have coronary occlusion a study of the electrocardiograms was rather inconclusive. In none of them were there significant alterations in the Q. R. S. complex, and in none were there changes in the T wave that corresponded to those described by Smith and others. From what evidence I have been able to collect I think that we are unable in cases of angina pectoris which do not show other signs of cardiac sclerosis to receive any constant help from electrocardiograms.

PROGNOSIS

In middle-aged persons with angina pectoris, even with negative cardiac and circulatory signs, the prognosis should be guarded. Middle age is the time when sclerosis of the blood-vessels begins to declare itself, and we know by experience that the coronary vessels may show decided changes which are not evident in the peripheral vessels. Pain in the middle-aged and elderly individual should always be taken very seriously by the physician, especially if the attacks persist after reasonable care and treatment. Attacks that come on at night are usually ominous. More than one instance has come to my notice where a physician, because of negative findings, has taken too lightly the evident history of angina pectoris in a middle-aged individual and has been chagrined by the sudden death of the patient within a few hours, days, or weeks of his statement that there was no cause for anxiety. When possible, some responsible relative should be informed of the gravity of the condition and should be made to understand the need of care. Sudden death comes as a great surprise to the friends when unprepared. Long intervals with freedom from symptoms may occur, and in true angina pectoris are difficult to understand. Sir Clifford Allbutt speaks of one case with an interval of eight years, but this is most unusual in coronary disease, in which attacks are apt to recur with increasing intensity. In 2 of my recent cases there were periods of freedom lasting one and one-half years.

Olser's statement that angina pectoris is an uncommon condition in hospital practice is true for this hospital, where only 13 cases have been seen in ten years, 11 males and 2 females.

TREATMENT

The treatment of angina pectoris may be divided into two parts: the care of the attack and the care of the underlying condition. During the attack the patient will usually rest, whether he has been advised to or not. The attack may be momentary, or it may last for several hours, or a day or two. Many of the attacks of true angina pectoris are relieved by a few whiffs of amyl nitrite. Where the attack is prolonged it may be necessary to use morphin. Rest and these two drugs will usually control the attack. If the attack is very severe the patient should be kept in bed for several days, at least a week. Morphin should be given, $\frac{1}{4}$-grain dose, and with it $\frac{1}{150}$ grain of atropin sulphate, to do away with any increased vagus inhibitory effect which the morphin might cause. After the attack is over all causes for *exertion or of mental strain* or excitement should be removed as far as possible. It should be remembered that emotion and excitement cause attacks of angina pectoris quite as easily as exertion. In most cases of severe angina pectoris the nutrition of the heart is so interfered with that more or less complete rest is indicated. Until the heart's power is estimated and a knowledge of the degree of reserve force is obtained, the patient should be kept constantly in bed. After improvement has clearly declared itself, then the patient may be allowed to go about, rising late in the morning, going to bed early, and conducting his affairs in such a way as to throw as little strain upon the heart and circulation as possible. In some of these patients the use of sodium nitrite three or four times a day in 1-grain doses has a very beneficial effect. Patients should also carry about with them pearls of amyl nitrite, because if an attack can be aborted the general effect on the patient is much more satisfactory. While the attack is on the distress is very great and many patients have a sense of impending death.

This can often be removed by using amyl nitrite as soon as the attack is felt approaching.

In middle-aged people, even in the presence of a negative Wassermann and negative syphilitic history, it is well to try antiluetic treatment.

Within a year Jonnesco (Bull de l'académie de Med., Paris, July 19, 1921) reports a second case in which he resected the entire cervical sympathetic chain on the left side to interrupt communication between the heart and aortic plexus and the nerve centers originating in the first and second cervical ganglia. The immediate results were excellent; the interval since the operation in his first case is now over five years and there has been no recurrence of the angina pectoria. Tuffier has also reported 3 successful cases. It is stated that suppression of the paroxysms of pain does away with the usual cause of the sudden death in the cases where the network of nerves is particularly close and the pain unusually severe. We have not had experience with surgical treatment, nor do we see how it can be of value in coronary angina pectoris. The work of Lewis and others in dogs shows an interference of the circulation and ventricular fibrillation as a cause of death. In 6 of our hospital cases with a clinical history of angina pectoris each had coronary sclerosis, and in some instances thrombosis at autopsy.

SUMMARY

1. The importance of distinguishing between the various forms of precordial pain.

2. Angina pectoris in young, middle-aged, and old individuals, with its several causes.

3. The great importance of recognizing by history and characteristics of the attack the presence of true angina pectoris in a person without evident cardiac signs.

4. The establisment of treatment as early as possible in cases with, and especially those without, cardiac signs.

CLINIC OF DR. ELLIOTT P. JOSLIN

NEW ENGLAND DEACONESS HOSPITAL

DIABETES: 1. DEATHS FOLLOWING SUDDEN CHANGES IN DIET. 2. DIABETES OF FIVE YEARS' DURATION IN A TEN-YEAR-OLD BOY

1. **Deaths Following Sudden Changes in Diet.**—Repeatedly your attention has been called to the occurrence of sudden death in diabetes. This may take place during inanition, particularly when the blood-sugar falls far below the normal level. A knowledge of the possibility of such a fall during inanition offers the means to avoid catastrophes of this nature through more frequent examinations of the blood of such cases. A second and rather more common cause of sudden death is angina pectoris, and against this one can guard only in so far as with the non-diabetic individual. Other forms of heart disease may be interrupted by sudden death, as in Case No. 870, who was operated upon for gall-stones recently, died unexpectedly seventeen days later, and at the postmortem examination was found to have an aneurysmal dilatation of the posterior wall of the heart. The duration of the diabetes in his case was seventeen years, and even if the operation had not been performed it is possible that the end would have come within a short period either from heart disease or a recurring infection of the gall-bladder. However, the sudden shock of his death emphasized the necessity for constant watchfulness of the circulation in all cases of diabetes.

But the third cause of sudden death in diabetes is far and away the most important, and it is diabetic coma. Though the percentage of patients dying from coma has decreased markedly in the last few years, it still remains the great menace to the diabetic, especially outside of hospital walls. Formerly two-thirds

of all my fatal cases succumbed to coma, but among the 536 cases of diabetes treated in hospitals since April 1, 1919, there were but 4 instances among 16 deaths, or 5, if a case complicated with pregnancy and pneumonia be included. Nearly 90 per cent. of all cases of diabetes who succumb to the disease during the first year of its duration die in this manner. This is most unfortunate, because the first year of diabetes should be the safest and the most efficient year for the patient, because the disease is at the beginning. One can hardly go so far as to say that all deaths from coma are needless, but each death of this type demands study in order that the causes leading up to it may be avoided in the future. For this reason I wish to add 2 more examples to those previously reported, and again point out that they followed the sudden restriction of carbohydrate. In addition, the first patient was given an exclusive protein fat diet, and the second patient was abruptly fasted without regard to the duration of the disease being five years.

Case No. 2496, a married woman of thirty-eight, was advised of the presence of sugar in her urine in January, but from her loss of weight the onset probably dated back to the preceding August. Within the previous two years there was no record of any urinary examination. As soon as the diagnosis was established the patient was placed upon a diet of 5 per cent. vegetables; in two days these were omitted and her food was limited to meat. Coma developed during the following forty-eight hours, and she was dead the next day. The entire course of the treatment of this case of diabetes was seven days instead of 5.3 years, which is the average duration of life of fatal cases of diabetes reported to the Board of Health in Boston in 1920. With the knowledge of this case fresh in mind do you wonder that you are urged to alter the diets of your patients slowly? It is possible that 98 cases out of 100 might not react to changes of diet in this fashion, but neither you nor I can afford to take that 2 per cent. chance. For your convenience until you have devised a method of your own I will pass around two cards showing test diets and maintenance diets given patients upon admission to this hospital and their explanation.

TABLE I

DIABETIC DIETS

Form J. 4. Thomas Groom & Co., Inc., 105 State St., Boston, Mass.

Diets with which to become Sugar free	Diet in Grams: Carbohydrate	Protein	Fat	Calories	Test Diets: Vegetable 5%	Orange	Oatmeal	Shredded Wheat	Uneeda	Potato	Bread	Egg	Cream 20% Fat	Bacon	Butter	Meat	Fish	Skimmed Milk	Name of Diet
T. D.1	189	89	15	1247	300	300		1		240	90					90	180	480	1
T. D.2	102	58	0	640	300	300		1		120							180	360	2
T. D.3	64	33	0	288	300	300				60							180	240	3
T. D.4	26	27	0	252	300	200											90	120	4
T. D.5	15	6	0	80	300	80													5
Maintenance Diets	**Carbohydrate (C)**										**Protein and Fat (PF)**								
C1 + PF1	10	11	6	138	300	100					1	1	60						1
C2 + PF2	22	18	18	302	300						2	1	60						2
C3 + PF3	32	24	24	440	600	100					2	1	60						3
C4 + PF4	42	29	30	630	600	200					2	1	60	30					4
C5 + PF5	52	33	43	813	600	200	15				2	1	60	30	15	30			5
C6 + PF6	63	43	55	1009	600	200	30				2	1	60	30	15	30			6
C7 + PF7	73	51	70	1126	600	200	30				2	1	60	30	15	30			7
C8 + PF8	83	59	87	1351	600	200	30				2	1	60	30	15	30			8
C9 + PF9	96	63	93	1469	600	200	30	½			2	1	120	30	30	30			9
C10 + PF10	107	63	93	1517	600	200	30	1			2	1	120	30	30	30			10
C11 + PF11	131	75	98	1706	600	200	30	1		120	2	1	120	30	30	120			11
C12 + PF12	155	79	98	1818	600	200	30	1		240	2	1	120	30	30	120			12

Food	Weight in grams	Approximate equivalent
Orange	300	One and one-half (large size)
5 per cent vegetables	300	Three moderate portions
Skimmed milk	480	One pint (16 ounces)
Potato	240	Two small portions
Potato	120	Two medium-sized potatoes
Meat	90	One moderate portion

Food	Weight in grams	Approximate equivalent
Bread	90	Three small slices
Oatmeal (dry wgt.)	30	One large saucerful
Bacon	60	Four tablespoonfuls
Butter	30	Four crisp strips
Butter	30	Three medium portions

The Test Diets are designed for the period during which the patient becomes gradually sugar free. On successive days advances can be made from Test Diet 1 to Test Diet 5, and if on the fifth day the patient is not sugar free, fasting can be employed for one or more days.

The Maintenance Diets are for use so soon as the urine of the patient is free from sugar. If this occurs as a result of Test Diet 5 the patient begins with Maintenance Diet C_1PF_1. The

TABLE I—*Continued*

Water, clear broths, coffee, tea, cocoa shells and cracked cocoa can be taken without allowance for food content.

FOODS ARRANGED APPROXIMATELY ACCORDING TO CONTENT OF CARBOHYDRATES.

5%	10%	15%	20%

* Reckon average carbohydrate in 5% veg. as 3%—of 10% veg. as 6%

	1%-3%	3%-5% *	10% *	15%	20%
VEGETABLES (fresh or canned)	Lettuce Cucumbers Spinach Asparagus Rhubarb Endive Marrow Sorrel Sauerkraut Beet Greens Dandelion Greens Swiss Chard Celery Mushrooms	Tomatoes Brussels Sprouts Water Cress Sea Kale Okra Cauliflower Egg Plant Cabbage Radishes Leeks String Beans canned Broccoli Artichokes canned	Str. Beans Pumpkin Turnip Kohl-Rabi Squash Beets Carrots Onions Green Peas canned	Green Peas Artichokes Parsnips Canned Lima Beans	Potatoes Shell Beans Baked Beans Green Corn Boiled Rice Boiled Macaroni
FRUITS	Ripe Olives (20% fat) Grape Fruit		Watermel'n Strawberr's Lemons Cranberries Peaches Pineapple Blackberr's Gooseberr's Oranges	Raspberries Currants Apricots Pears Apples Huckleberr's Blueberries Cherries	Plums Bananas Prunes

1 gram protein, 4 calories.
1 " carbohydrate, 4 "
1 " fat, 9 "
6.25" protein contain 1g. nitrogen.

1 kilogram=2.2 pounds.
30 grams g or cubic centimeters c c. =1 ounce.
A patient "at rest" requires 25 calories per kilogram

(30 grams 1 oz.) CONTAIN APPROXIMATELY	CARBOHYDRATES G.	PROTEIN G.	FAT G.	CALORIES
Oatmeal, dry wgt.	20	5	2	118
Shredded Wheat	23	3	0	104
Cream, 40%	1	1	12	116
" 20%	1	1	6	62
Milk	1.5	1	1	19
Brazil Nuts	2	5	20	208
Oysters, six	4	6	1	49
Meat (uncooked, lean)	0	6	3	51
" (cooked, lean)	0	8	5	77
Chicken (cooked lean)	0	8	3	59
Bacon	0	5	15	155
Cheese	0	8	11	131
Egg (one)	0	6	6	78
Vegetables 5% group	1	0.5	0	6
Vegetables 10% group	2	0.5	0	10
Potato	6	1	0	28
Bread	18	3	0	84
Butter	0	0	25	225
Oil	0	0	30	270
Fish, cod, haddock (cooked)	0	6	0	24
Broth	0	0.7	0	3
Fruit 10%	3	0	0	12

Thomas Groom & Co., Inc., 105 State St., Boston.

actual articles of food representing the carbohydrate in the diet for the first day are given under the heading of carbohydrate, for convenience described $C_{1, 2, 3}$, etc. The articles referred to under protein and fat are under that heading, which for the same reason is described as $PF_{1, 2, 3}$, etc. Certain cases of diabetes can proceed steadily day by day from C_1PF_1 to $C_{12}PF_{12}$, without showing sugar. If sugar does appear in the urine, drop back

two days in the carbohydrate group, wait till sugar free, then advance in the protein and fat group until sufficient calories are obtained. Thus, if sugar shows on C_7PF_7 the diet prescribed would be that included in C_8PF_7 and thereafter progression could be made in the PF group until 25 to 30 calories per kilogram body weight were furnished the patient.

Occasionally the patient becomes sugar free on Test Diet 2, 3, or 4. It is then unnecessary to begin with Maintenance Diet C_1PF_1. Instead begin with a maintenance diet which contains a value for carbohydrate similar to that of the test diet upon which the patient became sugar free.

If the protein and fat are too high for the individual on a given day it is easy to advance the carbohydrate and decrease to an earlier day on protein and fat.

The plan is arbitrary and the majority of cases will demand some modification. It is arranged to enable patient or nurse to see in advance the general plan of treatment.

Case No. 2546 discovered sugar in his urine in August, 1917, at forty-two years of age, when he was 26 pounds overweight. In the next three years, despite the diabetes, he became 41 pounds overweight. During the twenty-five years prior to the onset of his disease the urine had not been examined! He came to my office in March, 1922 and related that in the five years subsequent to the diagnosis of diabetes he had never been sugar free; yet it should be remembered that he had lived five years instead of dying seven days after the date of diagnosis, as did the last patient. In May, 1921 there was marked accentuation of his symptoms, and again in the last week of February, 1922. Two days before his visit he consulted a physician, who advised him to fast and drink whisky and water. In all his life he had never taken alcohol, but he followed his doctor's advice implicitly. Upon examination I found the patient thin, flushed, and the skin dry; the reflexes were normal, respiration was 19, pulse 84, blood-pressure 155/85, heart and lungs normal, liver just palpable. A subsequent ophthalmic examination by Dr. H. F. Root proved negative. He did not bring a specimen of urine, and, what is surprising in a diabetic patient, could void but a few

drops. This contained sugar and albumin, but no diacetic acid. The patient was sent home, with instructions to stay abed and to take a liberal quantity of carbohydrate in the form of cereal and fruit and an abundance of water. Notwithstanding this advice the inability to void urine persisted, and the next day he willingly entered the hospital. By catheter less than 10 c.c. of urine were obtained. The specimen was of alkaline reaction, had a large trace of albumin with many casts, no pus. The sugar amounted to 0.6 per cent. Diacetic acid was demonstrable. The few cubic centimeters of urine secured were quite insufficient for satisfactory analysis, but Dr. Horace Gray, at my office, and Dr. H. F. Root, at the hospital, examined the scanty specimens on these two days, and found the reaction of each to be alkaline despite the fact that the patient had acidosis as shown by the CO_2 in the alveolar air, 24 expressed in mm. Hg. tension, and although he was not taking alkalis. The patient was conscious, comfortable, had a moist skin, and his blood-pressure was 132/80.

For the two and a half days following admission every effort was made to promote urinary secretion. Liquids were given freely by mouth, by rectum, and subcutaneously. Heat was applied to the skin and it was easily kept moist. The diet consisted chiefly of oatmeal gruel, skimmed milk and orange juice, with a little albumen-water. Glucose[1] was added to the enemata, because so little food was retained by mouth. A duodenal tube was expelled. In other words, the routine treatment for acid poisoning and uremia was employed, but to no avail, and the man died, like the preceding case, within one week after a sudden change in diet.

Although the patient secreted practically no urine during the three and a half days under observation the course of his case could be watched by the changes which took place in the blood. These are shown in Table II. There it will be seen that the blood-sugar at my office was 0.48 per cent., and that it rose to 0.57 per cent. the day before death. The change in non-protein nitrogen was notable. From 0.107 per cent. on March

[1] Levulose would be preferable.

2d, it steadily rose to 0.175 per cent. on March 5th, and the urea to 0.116 per cent. on the same date. The values for uric acid and creatinin likewise were high, though the uric acid did not greatly change during the last two days. The creatinin, however, rose from 0.010 to 0.023 per cent. Throughout, the values for sodium chlorid in the plasma were low, and the fat in the blood at no time reached a value above 1.15 per cent. Although in the few drops of urine secured there was but a trace of diacetic acid, the CO_2 in the blood was constantly low, being on March 3d in terms of mm. Hg. 24, falling to 20 on March 5th. The acetone bodies in the blood, on the contrary, were high, varying between 0.098 and 0.085 per cent.

TABLE II

ANALYSIS OF BLOOD OF CASE NO. 2546

	Blood.								
Date.	Sugar, per cent.	N. P. N., per cent.	Urea N., per cent.	Uric acid N., per cent.	Creatin and creatinin, per cent.	NaCl, per cent.	Fat, per cent.	Acetone bodies, mg.	Plasma CO_2, mm. Hg.
6.00 P. M. March 3/22	0.48	0.108	0.072	0.007	0.010	0.462	0.97	..	24
9.00 A. M. March 4/22	0.50	0.125	0.073	0.010	0.013	0.405	1.15	..	24
3.30 P. M.[1] March 4/22	0.48	0.135	0.072	0.010	0.017	0.439	....	97	
10.30 A. M. March 5/22	0.56	0.157	0.108	0.011	0.021	0.429	1.10	..	21
10.30 P. M.[2] March 5/22	0.51	0.175	0.116	0.010	0.023	0.363	0.74	90	20

Several of your members had an opportunity to see this patient. You will recollect that his condition differed markedly from that of a case of diabetic coma. Although stuporous, he could be aroused even until shortly before death. There was no sign of anxiety. The respiration was quiet and at no time

[1] Plasma was separated immediately after venesection. Plasma was 68 per cent. of whole blood and corpuscle 32 per cent.

[2] The filtrate of this specimen was kept until the following morning. It was analyzed without formaldehyd having been added for preservation.

suggested air-hunger. The eyeballs were firm, not soft, and, as has been said, the skin was moist. Toward the end the blood-pressure fell.

This case is almost a replica of Case No. 1015,[1] an account of which was published in the hope of preventing a similar calamity. Let us all take it to heart, and *not change the diet of a diabetic suddenly.*

2. **Diabetes in a Faithful Boy.**—Case No. 1305. It is not often that you will have an opportunity to treat so faithful a patient as Thomas, whom you see today. He has just returned to the clinic for a blood-sugar test, having left the hospital two weeks ago. Thomas consulted me first on March 22, 1917, four days after sugar was found in his urine and only one month after the onset of polyuria—so observant were his family and Dr. William Mitchell, of Needham. This was a good omen.

Like so many diabetic children he led his class at school, a circumstance which has come to my attention so frequently that I shall soon feel compelled to publish all my data upon such coincidences. Even in the last two weeks two other children, six and eight years respectively, and noted in their families for mental brilliancy, have been brought to me, and but a week ago another was discharged from the hospital.

From the day Thomas first came to the office until the present time, so far as is known, he has never deliberately violated a dietetic restriction. During this interval of nearly five years he has been admitted to the hospital eight times, and has spent in all about half a year in the institution. Thomas is one of a family of 5 children, and while at home he has been forced to depend to a very large extent upon himself for his treatment. All his records are his own, and no patient has ever kept a neater or more accurate account of his case.

First admission: Thomas went to the hospital on the first day he was seen by me. At that time his height was 4 feet, 5 inches and his weight was 53 pounds. Six months earlier his weight was 70 pounds, but his height at that time was unknown.

[1] Ref. Joslin, Treatment of Diabetes Mellitus, Lea & Febiger, Philadelphia, 1917, 2d ed., p. 88.

The normal weight for a child of this age and height is 65 pounds. Physical examination revealed a slow pulse-rate, 68, signifying a low metabolism, but nothing else of account. Already his diet had been changed by Dr. Mitchell, and in consequence the quantity of sugar in the first specimen of urine obtained was only 0.2 per cent. Diacetic acid was barely demonstrable. The CO_2 in the alveolar air was 33 mm. Hg. by the Fridericia test.

TABLE III

CASE NO. 1305. AGE TEN YEARS. FIRST ADMISSION.

Date, 1917.	Urine.			C.	P.	F.	Cal.	Blood-sugar, per cent. fasting.	Weight, pounds net.
	Days on given diet.	Diacetic acid.	Sugar, gm. 24 hrs.						
May									
22–23	1	Sl+	0.6	5	3	0	32	....	53
23–24	1	0	0	0	0	0	0	0.09	53
24	1	0	0	10	5	0	60	....	52
25	1	0	0	20	10	0	120	....	52
26	1	0	0	30	26	13	341	....	54
27	1	0	0	41	30	26	518	....	55
28	1	0	0	52	33	39	691	....	55
29	1	0	0	52	27	49	757	....	55
30	1	0	0	62	39	60	944	....	55
31	1	0	0	62	47	65	1021	....	55
June									
1	1	0	0	62	47	70	1066	0.07	55
2	1	0	2	72	47	70	1106	....	55
3	1	0	0	11	23	35	451	....	54
4–7	3	0	0	52	44	70	1014	....	55
7	..	..	..	..	..	..	....	0.07	

Have done Benedict test. Signed, T. N ———.

Table III shows that for his evening meal on March 22, 1917 he was given a few grams of carbohydrate in the form of 5 per cent. vegetables, thus continuing the restrictions imposed by his home physician, and the following day was spent in fasting. Becoming sugar free immediately, thereafter the diet was gradually increased until he received approximately 40 calories per kilogram body weight. His own signature to the words "Have

done Benedict test" the day he left the hospital shows that already he had assumed responsibility for his own treatment.

You will note that he was kept only a fortnight at the hospital; that his diet was rapidly increased, first in the form of carbohydrate and protein, and later in the form of fat; that his protein did not exceed 2 grams per kilogram body weight; and that the total calories were limited to about 40 per kilogram body weight. Upon this diet his weight increased slightly and his blood-sugar remained slightly below the usual normal figure. Finally, you will observe that despite this normal blood-sugar no liberties were taken either with his carbohydrate or his calories.

TABLE IV

CASE NO. 1305. SECOND ADMISSION

Date, 1919.	Urine.			C.	P.	F.	Cal.	Blood-sugar, per cent. fasting.	Weight, pounds net.
	Days on given diet.	Diacetic acid.	Sugar, gm. 24 hrs.						
Nov.									
16–17	..	0	7						
17–18	1	0	0	0	0	0	0	0.21	62
18–19	1	0	0	0	0	0	0		
19–20	1	0	0	0	20	11	179		
20–21	1	0	0	0	34	16	280		
21–24	3	0	0	0	46	18	346		
24	..	..	..	..	..	..	....	0.14	63
24–26	2	0	0	0	46	18	346		
26	..	..	..	..	..	..	....	0.12	65
26–27	1	0	0	0	46	18	346		
27–1	4	0	0	0	52	37	541		
Dec.									
1	..	..	..	..	..	..	....	0.14	66
1–5	4	0	0	1	56	43	610		
5	..	..	..	..	..	..	....	0.13	
5–8	3	0	0	5	59	41	625		
8	..	..	..	..	..	..	....	0.12	64

The *second admission* was two and a half years later, November, 1919. He had gained 10 pounds. His blood-sugar was 0.21 per cent. Table IV illustrates the method employed at that

time to bring it down to 0.12 per cent. Carbohydrate was withheld from the diet and protein was gradually increased to 2 grams per kilogram body weight, and fat was slowly added as the blood-sugar decreased. Almost no carbohydrate was allowed, and even at discharge it amounted to but 5 grams. The reduction in blood-sugar apparently was brought about partly by the restriction of carbohydrate, but rather more by the restriction of total calories.

TABLE V

CASE NO. 1305. FOURTH ADMISSION

Date, 1920.	Urine.			C.	P.	F.	Cal.	Blood-sugar, per cent. fasting.	Weight, pounds net.
	Days on given diet.	Diacetic acid.	Sugar, gm. 24 hrs.						
June									
25–26	..	+	9						
26	..	..	..	..	..	..	....	0.24	69
26–27	1	+	6	0	30	0	120		
27–28	1	+	5	0	0	0	0		
28	..	..	..	..	..	..	....	0.22	68
28–29	1	0	0	0	0	0	0		
July									
29–3	4	0	0	0	30	0	120		
3–5	2	0	0	5	41	23	391		
5	..	..	..	..	..	..	....	0.22	66
5–11	6	0	0	5	38	19	343		
11	..	..	..	..	..	..	....	0.09	65
11–14	3	0	0	10	45	32	508		
14	..	..	..	..	..	..	....	0.07	66
14–18	4	0	0	15	55	61	829		
18	..	..	..	..	..	..	....	0.12	67
18–21	3	0	2	16	57	74	958		
21	..	..	..	..	..	..	....	0.12	65
21–22	1	0	0	0	0	0	0		
22–26	4	0	0	9	53	74	914	....	66

The *third admission* points no lesson.

The *fourth admission* was in June, 1920. The blood-sugar had again risen to 0.24 per cent., but the sugar in the urine, as is shown in Table V, amounted to but 9 grams. A still lower

caloric diet was instituted. Upon two days he was fasted, and his food consisted exclusively of protein for the remainder of the first week. This time the blood-sugar fell to normal in seventeen days. Thereupon the diet was increased and he was discharged with 30 calories per kilogram body weight, made up of carbohydrate 9 grams, protein 53 grams, and fat 74 grams.

The *fifth entry* was not significant.

In June, 1921 he returned to the hospital for the *sixth* time with a blood-sugar of 0.25 per cent., blood fat of 1 per cent., but the sugar in the urine, as at all previous admissions, was low, 0.1 per cent. There was slight acidosis. On this occasion prolonged treatment did not bring the blood-sugar to normal, although the total calories in the diet were kept low. The measures adopted, however, were by no means as rigid as on previous occasions. This raises the query as to whether it would not have been preferable to have adopted the routine which worked successfully at the second and fourth admissions. He was discharged with a high blood-sugar, with 0.5 per cent. sugar in the urine and a diet of carbohydrate 5 grams, protein 50 grams, fat 61 grams, making a total of 769 calories.

Passing over his *seventh* short stay of a few days in the hospital in October, 1921, he re-entered for the *eighth* and most recent time January 2, 1922. (See Table VI.) Acidosis was now marked by the ferric chlorid test, showing a positive reaction for diacetic acid, the ammonia amounting to 2.1 grams in twenty-four hours, and the Fridericia test, showing the alveolar CO_2 to be at 29 mm. Hg. pressure. The blood-sugar was 0.24 per cent. and the blood fat was 1.68 per cent., a little more than twice the normal value. He was too ill to be weighed daily. The carbohydrate in the diet was gradually curtailed, protein limited and fat excluded, and in two days the acidosis had essentially disappeared. From this point onward the diet was increased, but on account of the high blood-sugar the protein was kept low as well as the carbohydrate, and the calories were restricted. Yet he did not become sugar free and the blood-sugar remained high.

At this point it is worth while to diverge in order to empha-

TABLE VI

CASE NO. 1305. EIGHTH ADMISSION

Date, 1922.	Urine.			Ammonia.	C.	P.	F.	Cal.	Blood-sugar, per cent. fasting.	Weight, pounds net.
	Days on given diet.	Diacetic acid.	Sugar, gm. 24 hrs.							
Jan.										
2	..	+++	60							
2–3	1	+	83	2.1	51	10	2	262		
3–4	1	+	30	1.3	38	6	1	185	0.24	
4–5	1	Sl+	39	2.8	22	13	18	302		
5–6	1	Sl+	13	1.36	12	19	24	340		
6–7	1	Sl+	25	....	11	18	30	386	....	57
7–8	1	Sl+	10	....	11	18	36	440		
8–9	1	0	10	0.95	11	23	51	595		
9–10	1	0	16	....	12	29	51	623	0.31	58
10–11	1	0	18	....	4	5	16	180		
11–12	1	0	14	....	1	13	12	164		
12–13	1	0	7	....	3	19	39	339		
13–15	2	0	7	....	3	19	52	556		
15–18	3	0	14	....	3	19	64	664		
18–19	1	0	15	....	4	27	69	755		
19–20	1	0	17	1.3	2	7	10	126		
20–21	1	0	9	....	3	19	64	664	0.27	55
21–22	1	0	18	....	5	20	76	824		
22–23	1	++	26	1.8	8	24	68	740		
23–30	7	+	15	1.8	9	17	73	761	0.33	
30–31	1	++	8	0.88	0	0	0	0	0.23	55
Feb.										
31–5	5	+	14	....	10	17	73	765		
5–15	10	+	11	....	10	18	75	787	0.26	51
15–16	1	Sl+	10	1.1	5	13	55	302		
16–20	4	Sl+	9	....	8	16	87	879		
20–21	1	Sl+	6	....	4	13	53	535	0.23	
21–22	1	Sl+	3	....	3	9	36	372		
22–24	2	0	4	0.59	4	12	46	485	0.19	
March										
24–3	8	0	5	....	9	16	87	879	0.22	55

size the importance of creatinin as a confusing element in sugar tests. Both the twenty-four-hour specimens of the urine gave positive tests for sugar and also various morning specimens. Fehling's test likewise gave a positive reaction, but, on the

other hand, no sugar was obtained in the same specimen with Nylander's reagent. As you are aware, this reagent does not react with creatinin and uric acid. The urine was accordingly shaken with Lloyd's alkaloidal reagent, which is known to remove creatinin and uric acid, and the filtrate was then tested for sugar with all three tests—Benedicts, Fehling's, and Nylander's. All were alike negative. Therefore, in cases of undernutrition like the present one must remember the probability of a high excretion of creatinin and take measures to avoid the error of interpreting its presence as sugar.

Returning to the serious dilemma reached in the case it was decided to adopt the Newburgh-Marsh method of treatment. The carbohydrate was reduced to 5 or 10 grams, the protein to 0.7 gram per kilogram body weight, and the calories raised to 30 per kilogram. Although Thomas remained upon this diet for several weeks no twenty-four-hour specimen of urine became sugar free and the blood-sugar at no time fell below 0.19 per cent. On the other hand, the boy's general condition seemed improved, though he exhibited a slight acidosis as measured by the ferric chlorid test for diacetic acid, the Rothera test for acetone in the blood, and the Fridericia test for carbon dioxid in the breath.

Coincidently with the change to the low carbohydrate, low protein, and high fat diet various other expedients were adopted to improve the tolerance for carbohydrate: (1) For example, it was found that if the carbohydrate was given in five meals the sugar excreted was somewhat less than when it was taken in three meals, a procedure which Dr. Horace Gray found useful with some of my other cases. (2) The quantity of carbohydrate at breakfast was made distinctly less than that at any of the other meals. (3) Washed bran biscuits and washed vegetables were omitted because of the uncertain quantity of carbohydrate which they not infrequently contain, despite honest efforts at removal, and instead all carbohydrate was given in the form of such staple articles as lettuce and cream. Nevertheless, in the face of all these measures, sugar in the urine persisted and the blood-sugar remained high. There was but one encouraging

chemical sign to support the clinical improvement, and this was the fall of the percentage of blood fat from twice the normal to nearly normal.

Patients often become hospitalized, and as Thomas had been placed upon as satisfactory a diet as any of us could devise, it was decided, not without some misgivings, to send him home in the hope that the change from close observation combined with persistence in the diet, which had been so carefully planned, would prove advantageous. The result was fortunate. This morning, eighteen days after discharge, he returns to the hospital looking better and, *mirabile dictu*, his urine is free from albumin, sugar, and diacetic acid, his blood-sugar 0.08 per cent., his blood fat 0.70 per cent., and he has gained 5 pounds.

In this connection another similar example of extraordinary improvement outside of an institution may be cited—Case No. 866, who remained at the hospital for more than six months without ever attaining a normal blood-sugar. Finally, he went to sea on a lumber schooner, and lived strictly according to his carbohydrate, protein, fat, and caloric regimen, which on the schooner was almost entirely limited to cabbage, fish, and bacon. Upon this régime he also became sugar free and acquired a normal blood-sugar, which he demonstrated to us all in repeated tests when the schooner returned to Boston after an interim of four months.

Recurring to Thomas' case, one must not be too elated at his improvement. He has a pulse as low as 48 and his blood-pressure is 70/48. Were it not that he appears to be in such good condition and that his gain in weight seems to be largely an actual gain in body substance and not merely edema, there would be cause for anxiety at his blood-sugar having dropped to as low a value for him as 0.08 per cent. This might signify inanition in the last stages.[1]

This case demonstrates that persistence in a method of treatment which appears to be right, and yet does not at once yield good results, may in the end give relief to symptoms and

[1] He returned for a visit on April 11, 1922. The gain in weight has been maintained, blood-sugar 0.08 per cent. His appearance is improved.

enable the patient to become sugar free. It illustrates how essential it is to pursue a plan of treatment for weeks or even months before considering it of no avail. This is not an infrequent observation, although at present not supported by definite statistics. It is a tribute which one is glad to pay to Dr. Newburgh and Dr. Marsh, because I believe this to be the type of case suitable to the procedures they recommend. It shows that the presence of abnormal values for sugar in the urine and blood is not a contraindication to allowing a patient to go home. Continuance of treatment apart from constant supervision and thought of their case will often improve the condition of the diabetic. A prolonged hospital stay has not in my experience been good for diabetic patients.

Thomas has lived nearly five years since the commencement of his diabetes. At onset he was ten years of age, his height 4 feet, 5 inches, and his weight 53 pounds. Today he is fifteen years old, his height 4 feet, 10 inches, and his weight is 61 pounds. What Thomas has done largely by himself it should be possible for other children to do who are in more favorable circumstances, provided they are as faithful to the diet.

CLINIC OF DR. JOHN LOVETT MORSE

PROFESSOR OF PEDIATRICS, EMERITUS, HARVARD MEDICAL SCHOOL

CHRONIC INDIGESTION IN EARLY CHILDHOOD

THIS little boy is twenty-five months old. He is the only child of healthy parents, was born at full term, was normal at birth, and weighed 8¾ pounds. He was weaned after a few days because his mother had an abscess of the breast. He did not thrive until he was seven months old. At that time he was in fair condition and his digestion nearly normal. He continued to do well until he was eleven months old, when he weighed 18 pounds. At that time he was taking a whole milk mixture with dextrimaltose, oatmeal gruel, and a little potato. His appetite then became capricious and he stopped gaining. He soon after began to vomit, but vomiting was never a marked symptom. Diarrhea developed, which alternated with constipation. His diet was changed in many ways. At times he was given whole milk mixtures, at others cream mixtures. As it was believed that he was not able to digest fat, he was finally put on skimmed milk mixtures, and at one time on buttermilk. It was thought that the maltose-dextrin mixtures disagreed with him less than milk-sugar or cane-sugar. Various sorts of cereals had been tried. It seemed as if none of them agreed very well. It was thought, however, that strained oatmeal and barley agreed better than the wheat preparations. Beef juice, at one time, had seemed to disturb him a great deal. Egg always upset him. He was usually able to take some meat, but at other times it came through undigested. The fruit juices always increased the diarrhea.

During the last two or three months he has failed quite rapidly. He is able to sit up alone, but cannot stand on his

feet. He is very fussy, and unwilling to stay alone for a minute. He cries almost constantly unless he is wheeled about in his carriage. His mother says that "he hates himself and everybody else." His nights are very poor. His appetite is now very bad. He is not vomiting, but is having several very large, watery, loose stools daily. His mother says that they are at times so large that they wet not only his clothes, but the bed, and that at times, when he is lying on his back, his hair is wet by them. He has lost weight rapidly. His diet during the last few weeks has been buttermilk, oatmeal, farina, cream of wheat, macaroni, rice, zwieback, toast, white crackers, milk-toast, chop, white meat of chicken, steak, junket, and white of egg.

Physical Examination.—He is mostly abdomen, with a small chest and extremities hitched to it. He is, in general, much emaciated, but, as so often happens in these cases, his lips and nails are of good color although his skin is pale. The skin is dry and stays in folds when pinched up. His expression is that of the chronic cross invalid. The fontanel is closed and the head of good shape. The tongue is nearly clean and the throat normal. He has 16 teeth. There is no rosary and the chest is of good shape. The heart and lungs are normal. The abdomen is very large and tense. There is dulness in the flanks, which shifts slightly with change in position. There is no fluid wave. The rest of the abdomen is tympanitic. No masses are palpable in it. There is no visible peristalsis and rectal examination is negative. The liver, spleen, and kidneys are not palpable. The extremities are normal. There is no spasm or paralysis. The knee-jerks are normal. Kernig's sign is absent. There is no enlargement of the peripheral lymph-nodes. His weight varies between 14 and 15 pounds. The variation depends on whether his bowels have moved or not, a change of $\frac{3}{4}$ pound not being uncommon with a movement of the bowels.

His last stool is very liquid and almost fills a pint jar. It is yellowish brown and macroscopically shows a little mucus and some shreds. It is so acid that wet litmus-paper turns bright red when it is put in the bottle before it reaches the

stool at all. Microscopically there is no fat, but an occasional starch granule and many iodophylic bacteria.

The urine contains neither albumin nor sugar and is free from acetone and diacetic acid.

Diagnosis.—The enlargement of the abdomen and the shifting dulness in the abdomen suggest, if one is not familiar with this type of case, tubercular peritonitis. The history in this instance is, however, not at all like that in tubercular peritonitis. It is most unusual to have diarrhea of this type in tubercular peritonitis in childhood. Furthermore, he would almost certainly have died months ago if the symptoms were due to tuberculosis. When the intestines are dilated, as in this instance, and filled with watery feces and gas, the feces gravitate to the flanks and cause dulness there, and change their position with the position of the patient. In this instance there was no fluid wave, but in some cases of this type a fluid wave will be present, although there is no free fluid in the peritoneal cavity. Several tuberculin tests have been done on this boy, all of which have been negative. A negative tuberculin test does not positively exclude tubercular peritonitis, but makes it very improbable. The white count is 16,000, which is higher than would be expected in tuberculosis. The large size of the abdomen suggests the possibility of congenital malformation or acquired dilatation of the colon. Congenital malformation can be ruled out by the relatively late development of the abdominal distention. Acquired dilatation is possible, but the story is not characteristic of that condition. There is no visible peristalsis and the rectal examination is negative. Moreover, the physical signs in this instance are consistent with a general dilatation of the intestines, which is not uncommon in severe chronic disturbances of digestion in infancy and early childhood. A positive diagnosis of chronic indigestion seems, therefore, justifiable. Incidentally, it is noteworthy that, as is usual in such cases, there are no evidences of rickets or scurvy. Moreover, the urine, as is also usually the case, shows no evidences of irritation of the kidneys or of acid intoxication.

The diagnosis of chronic indigestion is, however, not sufficient

in cases of this sort. In order to treat these cases satisfactorily it is necessary first to determine, if possible, the cause of the indigestion, and particularly its type.

Normally the digestive powers are equal to the work demanded of them, that is, the digestion of the food. The equilibrium between the digestive powers and the work to be done by them may be disturbed in two ways: by a decrease in the powers of digestion or by an increase in the work to be done. Decrease in the powers of digestion may be due to overfatigue, either physical or mental, diseases outside of the digestive tract, and diseases of the digestive tract itself. Increase in the work to be done in digestion may be due to improper methods of eating, too much proper food or improper food.

The causes which produce a decrease in the powers of digestion should always be first investigated. In this instance overfatigue evidently played no part in the causation of the indigestion, although it is probable that physical overfatigue now exaggerates the condition. In early childhood the diseases which most commonly cause disturbances of the digestive tract are diseased conditions in the fauces, nasopharyngitis and pyelitis. These conditions are excluded in this instance by our examination; so also are all other diseases outside of the digestive tract. Primary disease of the digestive tract is very uncommon at this age. In most instances there are none or only slight pathologic changes in the digestive tract, the symptoms being due simply to disturbances of function. These disturbances are almost always secondary to disturbances originating in the contents of the tract as the result of improper food or bacterial fermentation. In this instance there are no evidences of anything more than a disturbance of function and dilatation of the intestines from the excessive formation of gas and the weakening of the intestinal and abdominal muscles.

It is evident that in this instance improper methods of eating had nothing to do with the onset or continuance of the disease. It also seems probable that his trouble was not brought on by too much food. On looking back over his story it does not appear that he was especially injudiciously fed. He was,

however, given potato many months earlier than is advisable, and was perhaps also given an excess of oatmeal at the same time. The mistake, if any, which was made was in trying too many kinds of food after his appetite became capricious and he stopped gaining. It is very difficult, however, for both parents and physicians not to do this when babies and children lose their appetites and stop gaining. The result is, of course, that the symptoms are invariably exaggerated. The proper line of procedure is always to cut down the food and to find out what food can be digested. When this is done the appetite will return and finally gain in weight will ensue.

In many mild cases of indigestion no special type of indigestion has been established. Treatment by the elimination of improper articles of food is all that is necessary and recovery is rapid. In most of the more severe cases, however, the conditions are more complicated, and an intolerance, more or less marked, for one or perhaps two of the individual food elements has become established. This intolerance may or may not be associated with fermentation in the intestinal contents as the result of abnormal bacterial activity. This fermentation may take place in any of the food elements, usually primarily in the carbohydrates or proteins and only secondarily in the fats. In this instance there can be no doubt that there is abnormal and very marked fermentation in the intestinal contents. The marked acidity of the stools shows conclusively that the fermentation is in the carbohydrates, not in the proteins. This conclusion is strengthened by the presence of iodophylic bacteria. It is probable that, as there are no fat or fat elements in the stools, there is at present no secondary fermentation in the fats. Moreover, recently he has had practically no fat in his diet. It is also evident that sugar is not the cause of the fermentation in this instance, because he has had no sugar except the small amount of milk-sugar contained in the buttermilk during the last few weeks. The fermentation must, therefore, be in the starches. The final diagnosis in this case, therefore, is chronic indigestion with fermentation, the fermentation being in the carbohydrates, especially in the starches.

In cases of this type it is of importance to determine whether or not the gas bacillus is the cause of the fermentation. This will be determined in this instance by the fermentation test. It is not probable, however, that the gas bacillus will be found to be the cause, because, when it is the cause of the trouble, the stools are usually green and contain more mucus than in this instance. (The fermentation test was carried out in this instance and was negative, showing that the disturbance was not due to this organism.) With our present knowledge it is usually impracticable to determine the exact type of fermenting organism if the gas bacillus can be excluded. The type of organism is, moreover, of little or no importance in pointing out the line of treatment. The kind of fermentation, whether carbohydrate or protein, is the important thing.

Treatment.—There is no place for the so-called "digestants" in the treatment of this condition. There is almost never an insufficiency of either pepsin or hydrochloric acid. Pancreatin is destroyed in the stomach. It is, however, of great importance to make life as easy for him as possible and to guard him against overfatigue, either physical or mental. This means the exercise of much tact and judgment on the part of his parents. On the one hand, they must avoid crossing him as much as possible, and yet must be careful not to spoil him. He must be kept as quiet as possible and yet not allowed to tire himself out by fussing and fuming because he is kept quiet.

The treatment consists almost entirely in regulation of his diet. This must be regulated along two lines. It must be such that he can digest it and such that fermentation cannot take place in it. Furthermore, he must be given enough of this food to cover, at least, his minimum caloric needs. Although we have no definite proof from our own observations that he cannot digest and utilize fat, it is almost certain, from our experience in the past and from what we know as to the frequency of secondary disturbances of fat digestion in carbohydrate fermentation, that he cannot take it. Fat must, therefore, be excluded from his diet. It is evident also that the pathologic fermentation in the intestinal contents must in some way be

limited. Theoretically it would seem as if this could be done in two ways: by giving bacteria to destroy or neutralize the action of the bacteria which are causing the fermentation or by cutting down or eliminating the food element or elements on which these bacteria are growing. Unfortunately, it is impossible to permanently implant any organisms in the intestines by giving them in the food. It is impossible to permanently change the intestinal bacterial flora by giving bacteria by mouth, although the flora may be temporarily somewhat modified if the bacteria are given continuously. The intestinal flora can be changed, however, by changing the composition of the food, that is, the flora may be changed from the acidophilic to the putrefactive by changing the composition of the food, and vice versa. Cutting down the proportion of the carbohydrates and increasing that of the proteins in the food changes the flora from fermentative to putrefactive, and cutting down the proportion of protein and raising that of the carbohydrates changes it from putrefactive to fermentative. In this instance, since the gas bacillus is not the cause of the fermentation, lactic acid organisms would do active harm. It is useless, therefore, to think of attempting to influence the fermentation in this instance by giving bacteria by mouth. It can be limited by regulation of the diet, that is, by cutting out the carbohydrates as far as possible and by feeding him on proteins. In this way, and in this way only, can the fermentative process in his intestinal tract be modified. It is not wise, however, to limit his diet entirely to proteins. There is, of course, little danger of the development of acid intoxication on an exclusively protein diet, provided no fat is given. It is, however, very difficult to supply a sufficient number of calories to a child of this age when proteins only are given. The starches and milk-sugar, which are slowly broken down and remain in the intestine for a long time, will certainly keep up the fermentation. The maltose-dextrin preparations, especially those containing the larger proportions of maltose, are less dangerous, because they are absorbed higher up. Better than these, however, are the sugars which contain a considerable proportion of glucose.

The most available of these is corn syrup. A small amount of this will usually be absorbed high enough up in the intestinal tract so that it will not produce any marked amount of fermentation. It will be advisable, therefore, to give him 1 ounce of corn syrup daily, increasing this to 2 ounces if possible.

The most suitable protein for a child of this age is the protein of milk. This must be given, however, without fat. In a condition as severe as this it is not sufficient to simply skim the milk. The fat must be taken out by centrifugalization. The amount of fat-free milk which can safely be given to him is limited because of the milk-sugar which it contains. It will probably not be wise to give him more than 1 pint daily. He can, however, be given the casein of milk in the form of cottage cheese made from centrifugalized fat-free milk. Most children take this greedily. Four tablespoonfuls a day will probably not be too much for him. Other proteins which he can have are the white of egg, either soft or hard boiled, beef juice, the white meat of chicken, the lean of mutton or lamb chops, and scraped beef. It is useless to give him broths, because they have practically no food value and incidentally stimulate peristalsis. Beef juice is of little importance because it contains only 10 calories to the ounce. It will probably be safe to give him the amount of meat corresponding to that in a small chop daily. This amount of food contains between 500 and 600 calories, an amount just about sufficient to cover his minimum caloric needs, but not enough for him to gain on. He will, however, not be at all satisfied with this amount of food and will want something more to chew. He can be given this in the form of diaprotein muffins and bread, which children usually like. They will also add something to the caloric value of the food.

Whether this diet will entirely agree with him, whether it is sufficient, and whether it will exactly meet the indications can only be determined by the careful study of his weight, symptoms, and stools. It must be changed and regulated from day to day as conditions determine.

It may be necessary to irrigate his colon and to give him

a cathartic from time to time. It is possible that bismuth may help him somewhat. The subcarbonate is preferable to the subnitrate, which sometimes causes intoxication.

Prognosis.—He will, in all probability, eventually recover entirely. His abdomen is not likely, however, to become much smaller, but in time he will grow to it. Recovery will, however, be extremely slow and a matter of years rather than of weeks or months. It will certainly be interrupted by relapses, some of which may be quite severe. His digestion will, if he recovers, as seems likely, eventually be as good as if he had never had this illness.

CLINIC OF DR. GEORGE R. MINOT

MASSACHUSETTS GENERAL HOSPITAL

A CASE OF ACUTE BLOOD LOSS DUE TO PATHOLOGIC HEMORRHAGE, WITH A CONSIDERATION OF BLEEDING FROM SURGICAL OPERATION IN SUCH CASES

The Case. Pathologic Physiology and Treatment of Acute Blood Loss. Blood Regeneration After Acute Blood Loss. The Effect of Transfusion on the Patient's Symptoms of Acute Blood Loss. The Patient's Blood-picture. Atypical Hemophilia as the Diagnosis of the Cause of Hemorrhage. The Effect of Transfusion on Checking Hemorrhage. Consideration of Bleeding from Surgical Operation in Hemorrhagic Diseases and Conditions.

I AM going to show you today a case that illustrates the importance of carefully studying patients before undertaking a surgical procedure, and discuss briefly certain aspects of acute blood loss and the anemia it produces. I shall indicate the nature of this patient's disease and the benefits of transfusion. I shall conclude my remarks by pointing out the value of a proper interpretation of the history and laboratory tests when operation is considered upon patients who may bleed.

The Case.—The patient is a boy aged fourteen, who gives the following history:

Three days ago he had his tonsils removed at a small hospital in the suburbs, where he has been until an hour ago. The operation was performed because he had been suffering from repeated attacks of tonsillitis. The tonsils are said to have been very large and filled with necrotic material. At the time

of the operation he did not appear to bleed abnormally, but ever since blood has more or less persistently oozed from the wounds. After twelve hours a large blood-clot formed in his mouth and the hemorrhage was checked for a while. However, following an effort to cleanse the mouth, the clot loosened and blood loss has continued, being particularly excessive in the past eighteen hours.

The boy appears sick, very pale, white, not sallow. There is a large amount of clotted blood about the mouth and nose. Blood mixed with saliva may be seen to drip very slowly on to the gauze held at his mouth. He is restless, breathing shallowly and rapidly, 35 times to the minute. His extremities are cold, yet he is perspiring freely. The pulse is thready and feeble and its rate 160 per minute. The systolic blood-pressure is 65 mm. of mercury, and the diastolic between 40 and 45. The hemoglobin is 45 per cent.

The patient presents the classical symptoms and signs of acute blood loss, and immediate suitable treatment for this condition is imperative and urgent. In consequence of acute blood loss there is a diminution of the blood volume which leads to decrease of blood-pressure and development of anoxemia. The immediate treatment of acute hemorrhage which is severe enough to threaten life, besides treatment to stop the blood loss, must be directed to the decreased blood volume. This is best restored by the transfusion of blood. A transfusion for this patient from a suitably tested donor is now being arranged for. While this procedure is being carried out I wish to review with you certain aspects of acute blood loss and the anemia that it produces. We shall then consider the cause of this patient's bleeding and other aspects of his case.

Pathologic Physiology and Treatment of Acute Blood Loss.—The fluids of the body are of the most vital importance. It is estimated that the fluid content of the body is 60 to 70 per cent. of the body weight. This fluid consists of the blood, the lymph, and the tissue fluid, as well as that within the cells. The organism strives to maintain a fairly constant quantity of total fluid and to guard its chemical and physical constitu-

tion in the various systems. The maintenance of optimum conditions for cellular activity by regulation of the tissue fluids, together with regulation of the total volume of the body fluids, is what enables all higher forms of life to live within their environment. The tissue fluids are of great importance. These are the last path for the transport of nutrient material to the cell and the first to receive their waste products. The blood usually occupies the first place in our minds, yet it is but one unit of the fluid system. It does, however, exert the controlling influence in the maintenance of function in the organism. The blood volume is about one-eighth of the total body fluid, or 5500 c.c. for a man of 70 kilograms. The plasma volume remains surprisingly constant in the normal individual; and even in disease variations from normal are not often great except in conditions where rapid losses of fluid occur.

When the body is confronted with loss of fluid, fluid is withdrawn from the tissues to the blood. This is done to maintain the higher centers at the expense of the tissues in general. Thus the individual cells suffer before the blood-plasma itself shows depletion. Following blood loss deficient amounts of oxygen, from lack of available hemoglobin, reach the tissues, and thus anoxemia results. The tissues likewise are depleted of their plasma colloids, which are protecting factors in the interrelations of the blood and tissues. Sudden changes in the colloidal environment of the cells probably injure protoplasm, while anoxemia may result in the production of poisonous products. Such changes in the tissues are important to recognize, but they are not to be looked upon as the chief cause of the production of the symptoms of acute blood loss.

The symptoms of the blood loss are not so much related to absolute lack of hemoglobin as to a diminution of blood volume and lack of utilization of the hemoglobin remaining in the body. In the case of acute hemorrhage dilution of the blood rapidly occurs by transfer of the tissue fluid to the vascular system, and the original volume of the plasma is promptly restored if the hemorrhage is not too great and if the supply of tissue fluids is adequate. The chief danger in acute hemor-

rhage is due to the rapidity with which the blood is lost rather than the amount that leaves the body. If hemorrhage occurs so suddenly that those compensatory mechanisms, such as vasoconstriction and tissue fluid dilution, cannot maintain the blood-pressure at a safe level, death ensues unless measures are taken to remedy the defects. The vasomotor mechanism which enables the vascular system to adjust itself to a small blood volume in order to maintain a normal pressure may be adequate for a period of time and then fail. Its failure, or the reduction of the blood volume below a certain level, will be evidenced by a drop in blood-pressure accompanied by the attendant difficulties which this failure of the circulation imposes upon the organism. The systolic blood-pressure is perhaps the best single indicator of the condition of the patient who is losing or has lost blood. A low blood-pressure is also characteristic of shock, a condition often complicating hemorrhage, and one in which decreased blood volume occurs. A considerable decrease of carbon-dioxid content and of alkali in the blood occurs as the result of acute blood loss coincident with the increased respiration. This leads to acapnia, and thus, as Yandell Henderson and his associates (Jour. Amer. Med. Assoc., 1922, 78, 697) have pointed out, that through the loss of red blood-corpuscles hemorrhage is a form of asphyxia.

After an acute hemorrhage the hemoglobin and red count will not fall until restoration of the plasma volume commences. Gradually, as the plasma volume is restored, there is a consequent dilution of hemoglobin and red corpuscles. Thus a falling hemoglobin percentage and falling red count after a severe hemorrhage are not to be looked upon as indicating further blood loss, but as indicative of a desirable dilution of the blood. The amount that the blood can be diluted seems to depend within certain limits on the total amount of hemoglobin remaining. When this amount is about 30 per cent. or below, the process of dilution is not able to proceed without the presence of more hemoglobin. Under such circumstances the body suffers fully as much from hemoglobin as blood volume deficiency.

The criteria upon which to judge the condition of the patient

are blood-pressure readings, hemoglobin determinations, and pulse- and respiratory rate. A very low systolic pressure, 70 mm., for example, indicates a great diminution of the blood volume. Subsequent determinations are valuable to indicate whether the reaction of the patient is favorable or not. Single hemoglobin estimations are of little significance. A stationary level of hemoglobin is undesirable, while a falling hemoglobin indicates a flow of fluids from the tissues to the circulation. The faster the pulse, the poorer is the state of the patient. Likewise, the more rapid and more shallow the respirations, usually the more critical is the condition of the patient, because of the decrease of carbon-dioxid content and alkali of the blood. When possible, the determination of the blood alkali from the carbon-dioxid content of the arterial blood will aid to estimate the prognosis.

It is to be emphasized that the immediate treatment of acute blood loss should be directed at the blood volume. Large amounts of fluids administered by the alimentary tract may often accomplish the purpose for which transfusion seems indicated. All cases, whether given transfusion or not, will be helped by giving by mouth or rectum large amounts of fluids. Blood substitutes, such as gum acacia suspensions, given intravenously can restore blood volume rapidly, and may serve to restore the circulation when the hemoglobin is not greatly decreased. No absolute indication for transfusion exists so far as the oxygen need is concerned if the total hemoglobin is above about 30 per cent. However, when blood loss is severe enough to threaten life, transfusion of blood is distinctly the most satisfactory and effective procedure; and transfusion becomes a necessity, not a choice, if the hemoglobin is 30 per cent. or below. There is no therapeutic procedure that so rapidly changes a picture of impending death to one of relative well-being as does transfusion after acute hemorrhage. The exact procedure to be adopted in each case depends upon the amount and rate of blood loss. If the loss is less than 1000 c.c., and the blood-pressure chart shows the systolic pressure to remain above 90, there are no positive indications for trans-

fusion or infusion. Even after larger losses nature alone may accomplish a satisfactory result. The dividing line between death and recovery after sudden blood loss is a narrow one, and a reduction of one-third of the blood volume is approximately the fatal point, though a reduction of this amount of hemoglobin is easily tolerated. Thus, when about 2 liters, or one-third of the blood volume, is lost, transfusion will give striking results and perhaps be actually life-saving.

A positive indication for transfusion is the known loss of over approximately 2000 c.c. of blood, or a persistently falling systolic blood-pressure, or one that remains below 90, together with no persistent decrease in the hemoglobin. Under such circumstances transfusion relieves the anoxemia, increases the blood volume, increases the output of the heart per systole, and thus restores the arterial pressure to a normal figure.

In any case of hemorrhage adequate consideration should always be given to the pulse- and respiratory rate and the patient's general appearance and condition, and to the location and character of the blood loss.

Cases of acute blood loss that are transfused appear to have their convalescence shortened and regenerate their blood more satisfactorily or sooner than similar cases that are not transfused. This effect of transfusion on the rate of convalescence should be recognized, and may be taken into account when one is considering the desirability of this procedure for its immediate beneficial effects in cases of acute blood loss. In many cases of hemorrhage there is doubt if transfusion is necessary. If there is considerable doubt, transfusion best be undertaken. In other instances where this doubt is not so great, the fact that though it may not be necessary it will probably shorten convalescence as well as improve the immediate symptomatology, will permit the decision to give the patient blood. It is, however, to be clearly recognized that transfusion is not necessary or definitely desirable in many cases suffering from relatively slight or gradual losses of blood, so that the procedure is not to be hastily recommended. Transfusion probably hastens convalescence of the patient with an anemia from blood loss

because a greater amount of hemoglobin in the body permits the different organs to function more normally than a lesser amount. Thus, with a greater rather than a lesser hemoglobin content of the body, there appears to be a more favorable situation created for the manufacture of blood. With a greater amount of hemoglobin the intensity of blood formation as reflected in the peripheral blood by the numbers of youthful red cells may not be so great as when there is a lesser amount, and one should recognize that excessive amounts of hemoglobin within the body can act to depress marrow activity.

In addition to the administration of fluids, and transfusion if necessary, a case suffering from blood loss should have suitable general management. He must be kept warm and have adequate rest, using morphin if necessary. The patient should be put as soon as possible upon a full high calorie diet, which should include a liberal amount of meat protein; but this should not be given to the exclusion of suitable amounts of carbohydrates, fats, salts, and vitamins. Clinically, it appears that cases with anemia due to blood loss definitely restore their red cells and hemoglobin faster on such a diet than on high calorie diets with small amounts of animal protein. This is in accord with the observations of Whipple and his associates, that following blood loss in animals a diet containing meat influences favorably blood regeneration.

Blood Regeneration After Acute Blood Loss.—Restoration of the plasma volume may be rapidly brought about after blood loss, but the restoration of the red cells and hemoglobin is a slow process, often requiring several months following a moderately severe hemorrhage. The regeneration of the blood begins rapidly. Within an hour a polynuclear leukocytosis develops, so that the total white count is often 20,000 per cubic millimeter a few hours after a hemorrhage. This may be dependent upon a rapid flow of tissue substances into the blood-stream which follows hemorrhage, carrying with it protein material which is known to induce leukocytosis. The increase of bone-marrow leukocytes in gradually decreasing numbers persists, however, from days to weeks. Their persistent increase is

indicative of active regeneration of the marrow elements called forth by the demand created by blood loss. Following the rise in white cells comes a rise in the platelets, so that after a few days it is not unusual to see four times as many platelets as normal, and these often of small size. This increase of these elements derived from the megakaryocytes of the marrow is a distinct feature of the blood in the anemia of acute blood loss. Gradually their numbers fall from the high level seen some days after hemorrhage, but they usually remain increased until the blood is essentially normal. Immediately after hemorrhage nucleated red cells and increased numbers of reticulated red cells (youthful red cells) may be seen. Their presence at this time indicates, as Drinker has pointed out, a thorough stirring up of the blood already in the body and are not necessarily related to the formative crises of the young cells seen later. Similarly, immature white cells, as myelocytes, may appear at such a time in the blood-stream. With the restoration of blood volume there develop increasing numbers of reticulated red cells, which then herald an increase of the red count. If the plasma volume is not adequately restored for some days, the height of the reticulated cells is delayed. Their appearance is relatively slower than that of the leukocytes and platelets. These formative crises of young red cells indicate a more rapid bone-marrow proliferation than the available marrow space permits, so that there is an alteration in the rate of delivery of the young cells into the circulation. If the alteration is abnormal enough, blasts and other immature bone-marrow elements may occur. Such crises of young red cells together with immature white cells may occur in any anemia. In the pathologic anemias, as pernicious anemia, in contrast to the anemia from blood loss, these crises often indicate a marrow dissolution or disintegration rather than a desirable marrow regeneration. Gradually, with the compensating growth of the marrow after blood loss, the young red cells decline in numbers, usually reaching near normal in from seven to fifteen days. Their numbers are somewhat related to the hemoglobin level. They decline as the hemoglobin increases, as

was pointed out when reference was made to the fact that transfusion may favorably affect blood regeneration in cases of anemia due to blood loss.

The restoration of the red cells, though a slow process, is more rapid than the restoration of the hemoglobin. Hence, achromia, which often increases in the first two weeks, and a low color-index are features of the blood-picture in convalescence. The red cells, besides showing achromia and evidence of youth (reticulation and polychromatophilia), will show an abnormal but not marked variation in size; their average size being smaller than normal, though true microcytes are not seen. Tailed and fragmented cells and true microcytes apparently are indicators of abnormal blood destruction. This process plays no part in the production of the anemia of blood loss. Thus, variation in shape of but only a relatively slight degree occurs.

At the end of a month after a moderately severe hemorrhage the patient will seem essentially well, but there will be unmistakable changes in his blood for a considerably longer period. It is important to recognize the slow but normal return of the red cells and hemoglobin because it indicates that the patient's activities during this period must be curtailed in order to enable him to obtain the most satisfactory return to health.

The Effect of Transfusion on the Patient's Symptoms of Acute Blood Loss.—The patient I showed you has been transfused with 1000 c.c. of blood from a healthy donor of the same iso-agglutination group. The donor's hemoglobin was 100 per cent. before transfusion. Besides transfusion the patient has received fluids by rectum and mouth, which will be continued in generous amounts in the coming twenty-four hours. From the considerations given above it is evident why it was desirable to give this patient a transfusion of blood. I now wish you to observe him again thirty minutes after his transfusion. His restlessness and sweating have ceased; his color has improved. The pulse, instead of being 160 per minute and feeble, is of good quality and now but 90. The respirations are deeper and have slowed to 22. The systolic blood-

pressure has risen to 110. The hemoglobin is 50 per cent. A general sense of well being has been substituted for a state of anxiety, and a condition of doubtful outcome has been turned to one having a much more favorable prognosis. The bleeding has stopped. The reason for this will be discussed later. The patient's improvement is due chiefly to the increased efficiency of the circulation from the increase of blood volume, as manifested by a higher blood-pressure, slower pulse-rate, and increased oxygen-carrying capacity of his blood. If the patient had had a normal blood volume of about 5000 c.c., and had received 1000 c.c. of blood with 100 per cent. hemoglobin, one would have expected a rise of 20 per cent. hemoglobin. His hemoglobin, however, has risen but 5 per cent. A greater rise has not occurred because with the increase of blood volume there has been plasma dilution, so that with the increased amount of fluid in the vascular bed each unit of blood contains less of the patient's own hemoglobin than before transfusion.

The Patient's Blood-picture.—The red count was not determined before transfusion, but now, after this procedure, it is 2,800,000 per cubic millimeter, and the hemoglobin is 50 per cent.

The blood-picture before transfusion, which is similar to that since transfusion, indicates that all three formed elements of the marrow are responding to the blood loss that has occurred in the past three days, and that the blood formation is proceeding at an increased desirable rate. The white count is 21,000 per cubic millimeter. The differential count of 200 cells is as follows:

Polynuclear neutrophils	80 per cent.
Large mononuclears	8 "
Lymphocytes	12 "

No eosinophils or basophils are seen. Some of the polynuclears are immature, as indicated by the few lobes to their nuclei. The platelets are 800,000; that is, more than twice their normal numbers. Many are small. The reticulated red cells are 10 per cent., and rarely a normoblast is found. The number of reticulated cells, as well as the platelets, may increase in the

next few days, and then gradually decline as the rate of emergence of the cells from the marrow approaches normal. If bleeding should recur, thus creating a further demand on the marrow, there will probably be further increases of these cells. However, if hemorrhage recurs the marrow responds less and less, so that the numbers of young red cells become fewer following repeated losses of the same amount of blood. This patient's red cells show very slight achromia and slight abnormal variation in size. There is little or no variation in their shape, and no microcytes occur. Polychromatophilic cells are evident in the stained preparation. The basophilic substance that causes reticulation and polychromatophilia is characteristic of young erythrocytes. Reticulated cells will always be found in considerably greater percentages than polychromatophilic cells, and are thus a more delicate indicator of the youth of the red cells.

Now that we know that the immediate danger to this patient from blood loss has been averted, and have learned that his bone-marrow is responding well, let us consider the cause of his hemorrhage.

Atypical Hemophilia as the Diagnosis of the Cause of Hemorrhage.—When a patient presents hemorrhage as a symptom it is always important to bear in mind that the bleeding may be due to a condition of his blood rather than to a local cause. When an operation is to be undertaken it is always advisable to know whether the patient is inclined to bleed abnormally. This may be learned from a properly interpreted history and physical examination together with the results of certain tests that should be made if blood abnormality is suspected. This patient complained only of recurring sore throats and had infected tonsils. He did not volunteer any further history. None other was inquired for previous to operation. On questioning him carefully the following information has been brought forth. He is an only child. Neither his father, mother, nor their brothers or sisters have bled abnormally. Nothing is known regarding the health of his grandparents. Twice—two years and four years ago—he bled profusely from his nose

following a mild injury. Several times in the past eight years, following relatively slight trauma, members of his family have observed that he developed very large black-and-blue spots "in the muscles of his legs." Twice without recognized cause he has had a lame thumb-joint that "became swollen and turned black and blue." Following a cut on his head five years ago, and removal of a loose tooth a year ago, he bled for over three hours. There has been no other bleeding and there is no evidence to suggest that petechiæ have ever been present. Except for the bleeding and recurrent tonsillitis he has never suffered from any ill health. His tendency to bleed abnormally has been considered insignificant by his parents and by himself and has caused no alarm.

The history, though not a striking one, of a hemorrhagic condition is, however, of importance and clearly suggests that he may be a hemophiliac. I have previously discussed[1] the differential diagnosis of certain hemorrhagic conditions, and thus will not consider at length the differential diagnosis of this case. The information regarding his previous health was obtained before transfusion, and the elements associated with pathologic hemorrhage, which I have also discussed,[2] were tested. The platelets, as we have noted, occurred in increased numbers, so that the diagnosis of one of the types of purpura hæmorrhagica need not be considered. The bleeding time was normal. Before transfusion the coagulation time of 1 c.c. of blood from the arm vein was twenty-two minutes, in contrast to the upper normal limits of about twelve minutes. The clot retracted normally and expressed a normal amount of serum. The reclotting phenomenon was present, but not marked. Hemorrhage tends to shorten the coagulation time, and it is possible that if this test had been performed before hemorrhage ensued the clotting time would have been found longer.

This boy's history, together with the prolongation of his clotting time, which indicates a pathologic condition of his

[1] Medical Clinics of North America, 1918, vol. 1, p. 1103.
[2] Ibid.

blood, enables one to diagnose the case as one of atypical hemophilia. A complete physical examination reveals no other abnormalities than those noted.

Typical hemophilia is an hereditary disease transmitted by the female and occurring in males only. The essential symptom of hemophilia is injury followed by bleeding which would not cause bleeding in normal persons. The cutaneous lesions are in the nature of bruises, and purpuric eruptions do not occur. Joint symptoms due to hemorrhage are a feature. The diagnosis of typical hemophilia should present no difficulties. Often the diagnosis can be made from the history of obstinate bleeding in males. The family history is of importance when it can be obtained with accuracy. Such information, together with a blood that presents formed elements in normal numbers and which gives a bleeding time within normal limits, but a coagulation time of several times normal, establishes the diagnosis. The mild cases of hemophilia, however, may not be recognized until some rather severe accident or surgical operation takes place. It is not a safe assumption that obstinate hemorrhages are due to hemophilia in the absence of evidence that the blood has an abnormally long clotting time. Cases designated as sporadic or atypical hemophilia undoubtedly occur in males in whom no family history of the disease can be obtained. These sporadic cases are usually much milder than those of typical hemophilia, in that obstinate bleeding is less pronounced, joint symptoms are rare, and the coagulation time of the blood less prolonged. The true nature of mild cases of the sporadic type with a relatively short coagulation time is often not recognized unless one carefully notes the symptoms and carefully determines the coagulation time by a suitable method. It is to this group of cases that our patient belongs.

The Effect of Transfusion on Checking Hemorrhage.—We may now consider why the transfusion has permitted the blood loss that has persisted for three days to cease. Transfusion was undertaken to increase the blood volume, to increase the oxygen capacity of the blood, to affect favorably blood regeneration, and for a fourth, most important, reason, to which

I have not yet referred, namely, to affect favorably the factors of coagulation. In hemophilia, prolonged coagulation time appears to be dependent on a qualitative deficiency of the blood-platelets, though their numbers are normal. Their numbers increase following blood loss in a normal manner. Transfusion of blood is the one method of supplying platelets. Thus, when this procedure is undertaken to remedy a defect in their numbers, as occurs in purpura hæmorrhagica, enough blood must be given to yield a sufficient number of platelets in the body to prevent bleeding. Likewise in hemophilia, where their character is altered, in order to check bleeding enough must be given to reduce the coagulation time to approximately normal. It is probable that other elements in normal blood favorably alter the factors of coagulation and thus assist to check hemorrhage particularly associated with a deficiency in the numbers or character of the platelets.

This patient's coagulation time is now, since transfusion, ten minutes. By its reduction to normal the bleeding areas are allowed to close, and thus the hemorrhage has been checked. The transfused platelets live but three to five days in the circulation, and as they disappear the coagulation time will become abnormally prolonged. Hemorrhage will then recur unless the wound has healed sufficiently. Further transfusion should be anticipated, for it is probable that before the wound has adequately healed the clotting mechanism will become again abnormal enough to permit bleeding from the injured surface. Further transfusion will permit for the time a return of the coagulation time to normal, and thus tide the patient over a suitable interval to allow the wound to heal and bleeding to cease. In the future hemorrhage from or into any part of the body will occur with sufficient trauma, as the effect of transfusion on the clotting mechanism is, as indicated, purely temporary.

Consideration of Bleeding from Surgical Operation in Hemorrhagic Diseases and Conditions.—This patient's catastrophe clearly indicates the importance of considering before any operation whether there is any reason to suspect pathologic

hemorrhage. A proper interpretation of the history is of the utmost importance. Bleeding from one source is much more usually due to local defects than dependent upon a pathologic blood. Patients should be questioned regarding any tendency to bleeding, including specifically asking if he bruises easily or ever has tiny red spots in his skin suggesting petechiæ. Likewise such lesions should be looked for upon making a physical examination. It is not unusual for individuals to exhibit petechiæ without knowledge of their presence. It is to be borne in mind that hemophiliacs do not develop petechiæ. Such lesions are features of cases with decreased numbers of platelets, but by themselves they do not signify that these elements are decreased. One should keep in mind, besides those cases who give a history of hemorrhage and who may bleed abnormally at operations, that there are certain types of abnormal bleeding that may occur at operation in spite of a previous negative history of hemorrhage; for example, cases of jaundice, particularly of the obstructive type, that have lasted for over three weeks, are prone to have prolongation in the clotting time of their blood, and may thus bleed excessively following a surgical procedure. If there is any reason to suspect a blood abnormality the more important tests for alteration of the blood-clotting mechanism should be properly and carefully performed. These tests are the bleeding time, enumeration of the platelets, determination of the coagulation time, with observations on the character of the clot, including its retractility. If all these tests are negative, an abnormal amount of bleeding from operation due to a pathologic condition of the blood practically never occurs. When an abnormal amount of bleeding does occur, and these tests properly performed have proved negative, it may be concluded that local conditions are responsible. Not only may the cause be referable to such an evident lesion as an untied vessel, but the lesions may be more obscure, among which may be mentioned the improper closure of capillaries due to anemia, alterations in the vasomotor mechanism, chronic inflammatory disease, and the presence of telangiectases. Telangiectases may give rise to profuse hemorrhage. They develop to a marked

degree in familial hereditary telangiectasia. In this condition there is no blood abnormality and abnormal bleeding only occurs from incision of the telangiectases.

It is important to realize that bleeding does not always occur when one of the tests on the blood is somewhat abnormal, and that prolongation of the coagulation time does not run parallel with spontaneous hemorrhage or the severity of the bleeding. It is a rather striking fact, as illustrated by this patient I have shown you, that markedly abnormal bleeding may occur with a relatively slightly delayed clotting time, while some cases of hemophilia with a coagulation time six times normal may not bleed profusely following slight abrasions or injuries. Marked prolongation of the coagulation time is, however, associated with considerable bleeding from surgical wounds. Slightly delayed clotting time is found in many conditions without hemorrhage and without serious hemorrhages following surgical operation. In lobar pneumonia prolonged coagulation time with rapid settling of the red cells is usual, yet hemorrhages are not associated with this condition. Certain types of endocrine disorders exhibit alterations in the clotting mechanism which are usually not associated with pathologic hemorrhage. The discrepancy between the degree of hemorrhage and the coagulation time when the other tests are normal indicates that the most important alteration in the blood that permits the excessive bleeding has not been demonstrated. It is probably dependent upon some abnormality of the colloidal state of the blood yet to be discovered.

In order to determine the degree of bleeding anticipated from operation the clinical symptomatology and the type of disease must be considered, together with the degree and character of the abnormality shown by the tests. The tests alone should not be the criteria upon which one should anticipate bleeding following incisions. However, they are to be looked upon as very important data on which conclusions are to be based. Cases of typical hemorrhagic disease, those with deficient numbers of platelets, as primary and secondary purpura hæmorrhagica, and those with a prolonged coagulation time, as hemo-

philia and hemorrhagic disease of the newborn, will certainly bleed abnormally from wounds. Jaundiced cases with prolonged coagulation time will bleed at operation roughly in proportion to the clotting time of their blood. Cases of atypical primary hemorrhagic disease are misleading as to whether bleeding will occur or not. The history in such cases is important. The patient I have demonstrated to you illustrates that cases of sporadic hemophilia, giving a history of little bleeding and of having a relatively slightly delayed coagulation time, may bleed fully as much at operation as a severe typical case with a very long coagulation time.

There is a condition seen, particularly in women, that may resemble chronic purpura hæmorrhagica. This condition, to which no exact name has been given, consists in the development of ecchymosis from slight trauma, particularly on the extremities. The condition is rarely marked, but mild cases are frequently observed, The patients usually state they bruise very readily and often without known cause. Like cases of chronic purpura hæmorrhagica, they are apt to exhibit black and blue areas on their arms and legs at any time; but, unlike purpura hæmorrhagica, they do not bleed from mucous membranes or develop petechiæ. The blood presents no abnormality, in contrast to that of purpura hæmorrhagica, and hence in the former condition abnormal bleeding does not occur from wounds.

Cases of idiopathic purpura (purpura simplex, purpura arthritica, Henoch's purpura) and those with simple symptomatic purpura, as develops in infections and intoxications, do not appear to bleed with incisions. This may be explained because the bleeding that occurs is rather particularly dependent upon local blood-vessel disturbance, though probably some unknown type of blood defect is present. Bleeding at operation in secondary hemorrhagic states, not purpura hæmorrhagica, such as those dependent upon hepatic disease, sepsis, chronic nephritis, myelogenous leukemia, polycythemia, poisons, etc., is to be foretold by the history and study of the blood.

In any given case it seems that if one of the tests referred

to above is slightly abnormal and there has been no hemorrhage, or hemorrhage from one source believed to be due to local cause, it is most unlikely that serious hemorrhage will occur with operation. If, however, several of the tests are slightly abnormal, particularly with a history of bleeding, bleeding is certainly more likely to occur at operation than when there is but slight abnormality of one of the tests. A good illustration of this is as follows: In some simple symptomatic anemias, particularly those associated with chronic focal sepsis, the platelets may be somewhat diminished, but not to the level usually associated with spontaneous hemorrhage as seen in purpura hæmorrhagica. In the same case the coagulation time may be slightly prolonged. There may be a history of some hemorrhagic tendency. In such a case, with or without a positive history suggesting an abnormal degree of bleeding, slight abnormal bleeding is apt to occur with operation.

It is not possible to formulate absolute rules as to whether hemorrhage will or will not occur with operation. However, a careful analysis of the history and examination of the patient, together with a clear conception of the symptomatology of the different hemorrhagic conditions, as well as proper performance of the simple blood tests, will serve as excellent guides. Exceptions to the general statements given above may occur, but become very few when cases are carefully studied. The exceptions may be that the tests are abnormal and the patient has hemorrhagic symptoms, yet bleeds little at operation; or the tests may be normal and the symptoms few, and the patient bleed abnormally. The former condition is distinctly more usual than the latter.

The site of operation will have an influence on the amount of bleeding. There will usually be more bleeding from a nasal operation than from an abdominal one. This is probably because the soft tissues contain a greater amount of thromboplastin, tissue juice, than the bony structures and mucous membranes. Thromboplastin is a substance which markedly accelerates coagulation. In some cases, as those of chronic

focal sepsis, with bleeding from one source, the bleeding may be due to the local conditions, but enhanced by the effect of this condition of the blood. In such instances surgical treatment of the local condition with proper precautions will improve the patient as well as his blood.

When operation is to be done in the face of a distinct abnormality of the blood which can permit hemorrhage, the patient should be transfused shortly before operation. Retransfusion should be anticipated and performed if bleeding ensues. This will enable the patient's blood to remain in an essentially normal state during the time that the tissues heal. In obstructive jaundice the administration of large doses of calcium and perhaps preparations of bile should be given for several days before operation. Such therapy may improve the coagulation time enough to prevent abnormal bleeding, due to the deficiency of the available calcium in the jaundiced case. Such treatment is of no value in other hemorrhagic conditions. If after this form of therapy in jaundiced cases the coagulation time is still considerably prolonged, transfusion should be undertaken before operation. If it is but slightly delayed, transfusion should be resorted to after operation if bleeding becomes at all alarming. In any given case if abnormal hemorrhage is considered possible from a surgical procedure, in contrast to highly probable, transfusion should be arranged for, but not performed unless it becomes necessary after operation.

CONTRIBUTION BY DR. CYRUS C. STURGIS

PETER BENT BRIGHAM HOSPITAL

A CLINICAL STUDY OF MYXEDEMA WITH OBSERVATIONS OF THE BASAL METABOLISM[1]

THOUGH the symptoms and general appearance of a patient with the disease myxedema are often very characteristic and striking, it is a condition which is frequently overlooked. The failure to recognize the true nature of a condition which incapacitates an individual, and may lead to serious mental change or to a fatal issue if untreated with its specific drug, constitutes a grave error on the part of the physician to whom the patient comes for relief. That this error occurs not infrequently is shown by a consideration of the preadmission diagnoses of these patients entering this hospital, which indicates that many of them have been treated, often over a period of several years, for "nephritis" or "anemia" rather than myxedema. An incorrect diagnosis frequently results not from the physician's lack of knowledge concerning the disease, but because the condition is rare and hence it is not considered as a possibility. The ease with which the syndrome is recognized when the typical features are present was illustrated by one of our former patients with myxedema, who observed that her brother had many complaints resembling her own, and hence correctly concluded that he had a similar ailment and brought him to this hospital for treatment.

There are, however, some patients with early, mild, or atypical types of myxedema wherein the symptoms and signs may be very suggestive, yet it is impossible to state with assurance from the history and physical examination whether the

[1] From the Medical Clinic of the Peter Bent Brigham Hospital.

patient has or has not the disease. It often happens, moreover, that many of the symptoms of myxedema are present, to a certain extent, in patients suffering from other diseases, and it is doubtless true that an incorrect diagnosis of myxedema is more frequently made than the failure to recognize it in a patient who presents its classical characteristics. Since the introduction of the determination of basal metabolism as a clinical test, and the recognition that the metabolism in myxedema is abnormally low, a greater accuracy may be hoped for in the diagnosis of the disease.

This study is based on a series of 15 patients who have been on the medical wards of the Peter Bent Brigham Hospital and in whom a definite diagnosis of myxedema has been made and substantiated by a consideration of the history and physical examination, basal metabolism studies, and in almost all instances by the beneficial effect following the administration of thyroid gland tablets. A number of these patients have been followed over a period of several years, and it has been possible to obtain metabolism studies at intervals, along with data on changes in the body weight, pulse-rate, and general condition of the patient. It was thought worth while to present these cases from a clinical aspect, as well as to record the metabolism observations and to emphasize the usefulness of the latter as an aid to diagnosis and a guide to thyroid therapy.

The course of the disease with the development of the typical clinical picture and the more detailed description of its major symptoms and signs is best presented by a consideration of the 3 case histories which follow:

S. H. V., Med. 15,108, age forty-two, was admitted December 21, 1920, complaining of "weakness and ease of fatigue."

Family History.—Father died at the age of thirty-six years of "stomach trouble." Mother living and well. Four brothers living and well. There was no history of thyroid disturbances in the family.

Past History.—In general, the patient's health had been excellent and "he never knew what it was to have a sick day" until the present illness. He had the ordinary diseases of child-

hood, but was not seriously ill with these, and made good recoveries without complications. For three years he had been working in the packing room of a publishing house, where he prepared packages for shipment and was required to lift packages weighing from 1 to 70 pounds. He had lost only a few days' work at intervals, and continued working up until the day of admission to the hospital.

Present Illness.—The earliest symptom dates back to a year and a half ago, when the patient realized that he was unusually tired after a day's work; this sensation was entirely new to him, as he had been a very robust man and a vigorous worker. This ease of fatigue was his chief complaint and gradually became more marked, though it did not prevent him from working. About this time the patient and his family noticed a definite change in his disposition. Previously, he had been a good-natured, lively individual, joking a good deal, often attending baseball games, and enjoyed visiting with his friends. With the onset of his illness he became surly, irritable, worried greatly over trifles, preferred to remain at home, and, as he expressed it, became a "grouch." He also noticed that he was not as alert mentally as he had been; it required longer for him to think of things, and his memory became very poor. Since the onset he noticed that the skin of his hands had become very rough and dry, and about six months before admission he realized that the skin of the entire body had undergone a similar change. His finger- and toe-nails became very brittle, so that, instead of cutting his nails, he broke them off. For the past year and a half he had observed that his hair had been falling out rapidly, particularly over the ears. There had been a definite change in the patient's features since the onset, so that even his friends failed to recognize him. His face became "larger" and rather marked puffiness developed about the eyes. At times his appetite was fair during his illness, though frequently there were intervals when he did not care for food and he was obliged to force himself to eat. He weighed himself frequently during the past three years and found that his average weight was between 175 to 178 pounds, but at one time

during that period he weighed 185 pounds for a short period. He became very slow at his work, and observed that the movements of his fingers became progressively more awkward; this was particularly apparent when he tried to tie up packages in his work. He also developed an awkward, shuffling gait, which became noticeable to his family. His voice normally was moderately high pitched, but during his present illness it became low pitched and husky, and his speech slow, monoto-

Fig. 235.—S. V. (M. 15,108). Patient presenting the typical appearance of myxedema. Note the characteristic border band of alopecia extending over the ears and in the suboccipital region.

nous, and hesitating. As a result of these changes it was often difficult for the members of his family to understand him. Throughout his present illness he has had a great deal of difficulty in keeping warm and often experienced "chilly sensations." On account of the sensitiveness to cold he objected to having a window open in the house, and at night required so many bed covers that his wife frequently commented about it. During the warm weather he did not perspire, although previous

to the present illness he perspired very easily. Recently he has had mild frontal headaches, though he has not observed any generalized aches or pains.

Physical Examination.—Showed a well-developed and nourished man, who spoke in a low, hoarse voice and in a monotonous, drawling manner. His face, well rounded, with few wrinkles, and with puffiness under the eyes, presented the typical appearance of myxedema (Fig. 235). There was a curious yellowish tint to the skin not unlike that seen in pernicious anemia, but differing in that this color was not seen in the conjunctivæ. The hair of the head was rather fine and was not brittle. The most striking thing about the hair was the border band of baldness about 1½ inches wide which extended from the suboccipital region behind to just above both ears. The hair in the pubic region was scant, but the eyebrows appeared normal. The skin, particularly of the hands and forearms, was very dry, rough, inelastic, and parchment-like. A smooth, firm, non-pitting, brawny swelling of moderate extent involved both lower legs. Previous to thyroid medication the patient's temperature was constantly subnormal, varying between 98° and 96° F. by mouth. The pulse averaged between 60 and 80 per minute on the ward, and the resting pulse was found to be 58 per minute.

Urine Examination.—Albumin, 0. There were a few brown granular casts and an occasional white blood-cell.

Blood.—Red blood-cells 2,680,000, hemoglobin 70 per cent., white blood-cells 7900.

Differential Count.—Polymorphonuclears 62 per cent., lymphocytes 36 per cent., large mononuclears 2 per cent. The red blood-cells appeared pale, but otherwise normal.

Metabolism Determination (Before the Administration of Thyroid Tablets).—38 per cent. below average normal.

Gastric Analysis (January 2, 1921).—Fasting contents 15 c.c. of bile-tinged, watery material obtained. Free HCl 0, total acidity 8. Three specimens were then removed at forty minute intervals following the administration of a test meal consisting of a slice of bread and a glass of water.

Specimen.	Free HCl.	Total acidity.
I	0	14
II	0	16
III	0	28

Twenty-three days later, after the patient had been given thyroid tablets, a second gastric analysis was performed, and the following results were obtained:

Fasting contents: 40 c.c. watery material obtained. Free HCl 0. Total acidity 9.

Specimen.	Free HCl.	Total acidity.
I	6	32
II	0	16
III	0	16

These results indicate, then, only an insignificant change in the hydrochloric acid content of the gastric juice following the administration of thyroid tablets for a period of twenty-three days.

Clinical Course.—The patient was given thyroid tablets 0.13 gm. twice a day, which was followed by a marked alteration in his appearance, particularly of the face (Fig. 236) and a disappearance of his symptoms. There was a remarkable regrowth of hair, and in about two months the blood-picture returned to normal. The patient resumed his former work and since then has not missed a day on account of illness. Figure 237 indicates the changes in the weight, resting pulse, and metabolism.

D. A. Mc., Med. 16,750, age forty-three, single, a statistician, was brought to the hospital on March 16, 1921 by his sister (L. B. C., O. D. D., 35201), who had been in the Out-door Department of this hospital several years previously, and in whom a diagnosis of myxedema had been made. The sister had recognized the condition in her brother and brought him to the hospital for treatment. The chief complaint of the patient on admission was "chilly sensations."

Family History.—The patient's father, mother, 2 sisters, and 2 brothers were living and well. One sister, mentioned above, came to the hospital in January, 1917, with the history

that she had noticed swelling of the face for three or four years, and at intervals had observed a yellowish tinge to the skin which she thought was "slight jaundice." For about three years, in addition, there had been intermittent swelling of the hands, feet, and body. She presented the typical appearance of myxedema, the basal metabolism was found to be 24 per cent. below normal, and complete relief followed the administration of thyroid tablets. There was no other family history of thyroid disorders.

Fig. 236.—S. V. (M. 11,708). The same patient as shown in Fig. 235 after eight and a half months of thyroid therapy. Unfortunately, this profile view was taken with the patient's face in the opposite direction from Fig. 235. The band of alopecia, shown in Fig. 235, was, however, the same on both sides, and the growth of hair shown in Fig. 236 was likewise equally great on the two sides.

Past History.—In general, the patient has always considered himself strong and healthy prior to the present illness. He was born of American parentage in Massachusetts, and has always lived in the eastern part of the United States.

Present Illness.—The onset of the present illness was so insidious and gradual that the patient was unable to state accurately just when the initial symptoms appeared. As near as he can remember, the first indication of the disease was

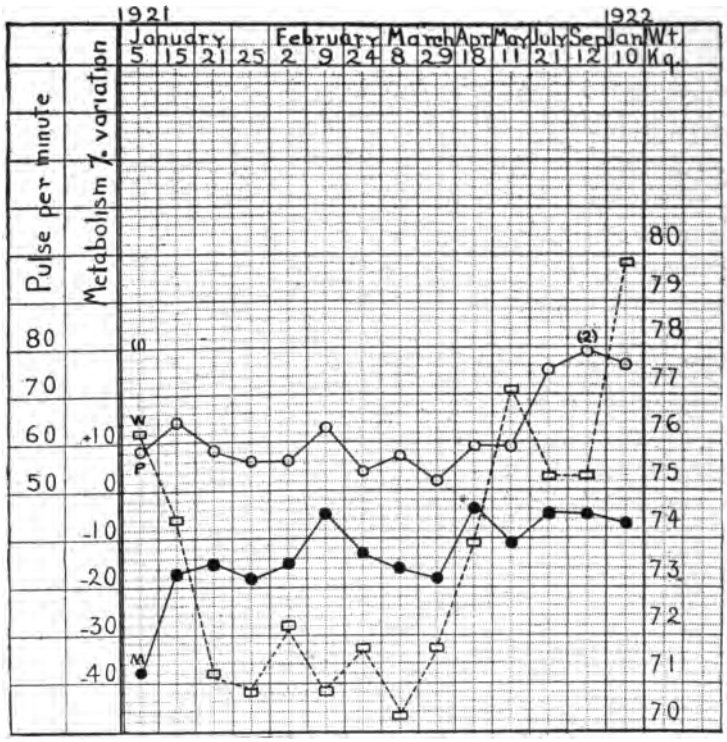

Fig. 237.—S. V. (M. 15,108). *P*, Pulse-rate; *M*, metabolic rate; *W*, weight in kilograms; (1) date on which photograph (Fig. 235) was taken before thyroid feeding; (2) date on which photograph (Fig. 236) was taken after thyroid feeding. The patient was given 0.13 gm. b. d. from January 5, 1920 until February 2d, and with this his weight decreased and the metabolism rose to a level which averaged about 15 per cent. below normal. Following this the dosage was changed at intervals until July 21, 1921, when the amount was fixed at 0.39 gm. alternating with 0.26 gm. q. d. This dose kept his metabolism constantly within normal limits, and hence is considered to be the proper maintenance dose. Note the rapid loss of weight of 5.9 kilos following the thyroid therapy. This was, however, followed by an increase in weight of 9.5 kilos, which is a gain of 3.6 kilos over the initial weight when the patient was first seen. This rapid gain in weight, following the initial loss due to the administration of tablets of thyroid gland, occurs not infrequently in patients with myxedema, and is probably due to the marked improvement in the general condition of the patient. This phenomenon is significant if one is utilizing the weight curve as a guide to the amount of thyroid gland to administer, for under these circumstances the gain in weight would erroneously be interpreted as an indication for an increased dosage, which might be injurious to the patient.

puffiness under the right eye, which he thought became apparent about six years ago. This was rapidly followed by the appearance of a similar condition in the left eye, and soon the upper lids of both eyes became swollen and the palpebral fissures small. At about this time his friends remarked that his "face was beginning to fill out," and suggested that he take more exercise. Following this advice he took long walks, but his condition did not improve. From the onset of his illness he noticed that he was extremely sensitive to cold, and as a result he often required extra blankets at night to keep warm, even during moderate weather. Since the onset of the disease he has never perspired, even when indulging in exercise which caused other people to perspire freely. In the warmest weather, when working in Washington, D. C., he always wore a coat and vest, yet felt perfectly cool. About six years ago his hair began to fall out more noticeably in the suboccipital region and behind the ears, and about eighteen months before admission the hair over his legs, arms, chest, abdomen, and axillæ began to disappear so rapidly that in a very short time there was very little hair in these regions, whereas previously it had been abundant. About two years after the onset his skin became extremely dry and scaly, and he observed that following a bath, or if he would rub his hands several times over his arms, the floor would be literally covered with scales. Beginning three years ago he gradually developed ease of fatigue and a very marked change in his mental attitude toward his work and social activities. Previously he had been an energetic, enthusiastic, ambitious individual with considerable pride in his work and a liking for outside sports such as baseball and fishing. As the disease progressed he found that tasks which previously took a very short time, now consumed hours, and frequently he was unable to finish them at all. On account of his lack of mental activity and extreme slowness in accomplishing any work he was obliged to give up his position one year previous to his admission to the hospital. He likewise lost all interest in outdoor sports and social activities, and preferred to remain at home rather than make the necessary

effort to go out and enjoy himself. Three years ago his voice became rather hoarse and low pitched and his friends remarked that he spoke in an abnormally slow monotone. Also at this time his hearing, which had previously been very good, became impaired, and this was particularly noticeable when he talked over the telephone. In the past four years there has also been a complete loss of sexual desire. When the patient first came to the hospital his weight was 150 pounds, which is the most he had ever weighed. At intervals during his illness he had consulted a physician who had apparently failed to recognize the condition, as thyroid extract had not been prescribed.

Physical Examination.—Showed a well-developed and nourished man. One was immediately struck by the appearance of the patient's face, which was full and without expression (Fig. 238). The nose and lips were thick and coarse and there was considerable swelling of both upper and lower eyelids, which caused narrowing of the palpebral fissures. The hair over the vertex of the skull was absent, and there was a characteristic "border band of alopecia" in the suboccipital region and over the ears. The hair of the body was practically absent, there being only a few hairs in the axillæ, the pubic region, and over the lower part of the sternum. The skin was extremely dry and desquamating and its surface temperature was below normal. Neither the isthmus nor either lobe of the thyroid gland were palpable. Blood-pressure was 95 systolic, 50 diastolic.

Blood.—Hemoglobin 70 per cent. (Sahli). Red blood-cells varied from 4,280,000 to 3,876,000. White blood-cells, 6800 to 7800.

Differential Count.—Polymorphonuclears 62 per cent., lymphocytes 35 per cent., large mononuclears 3 per cent. No abnormality was observed in the size, shape, or color of the red blood-cells. Blood Wassermann negative.

Urine Examination.—Yellow, clear, 1026 to 1018. Sugar, 0. Albumin, 0. Sediment, few hyaline and pale granular casts and occasional leukocyte. Phthalein test, two hours, ten minutes, 40 per cent.

Gastric Analysis.—Fasting contents 8 c.c., free HCl 18,

total acidity 26. Three specimens were removed at forty minute intervals following a test meal consisting of a slice of bread and a glass of water.

Specimen.	Free HCl.	Total acidity.
I	12	24
II	0	8
III	0	11

Basal metabolism on March 23d was 40 per cent. below the average normal.

Clinical Course.—The patient was given thyroid extract and the effect on the metabolism, pulse-rate, and body weight

Fig. 238.—D. A. Mc. (M. 16,750). Severe myxedema with the characteristic facial appearance, and typical loss of hair over the ears, the head, and the body.

is shown in Fig. 240. The change in the appearance of the patient is well shown by a comparison of the photographs taken before and after thyroid medication (Figs. 238, 239). The patient's symptoms have all disappeared, and he is at present

managing a small farm in New England and is able to do any kind of heavy labor.

J. F. B., Med. 16,697, a bookkeeper, age forty-eight years, was admitted to this hospital August 25, 1921, complaining of "lack of energy."

Family History.—Father died of pneumonia at the age of thirty-seven years. Mother died at the age of seventy years,

Fig. 239.—D. A. Mc. (M. 16,750). The same patient as in Fig. 238 after the administration of tablets of thyroid gland for five and a half months. The growth of hair is well shown over the sternum and in the left intraclavicular region in the picture on the right.

and one brother died, both of unknown causes. Two sisters were living and well.

Past History.—The patient had always been a strong, healthy man prior to the present illness, and does not recall having had any sickness. He had always been athletic, having acquired considerable local fame as an amateur heavy weight boxer.

Present Illness.—It was difficult for the patient to say

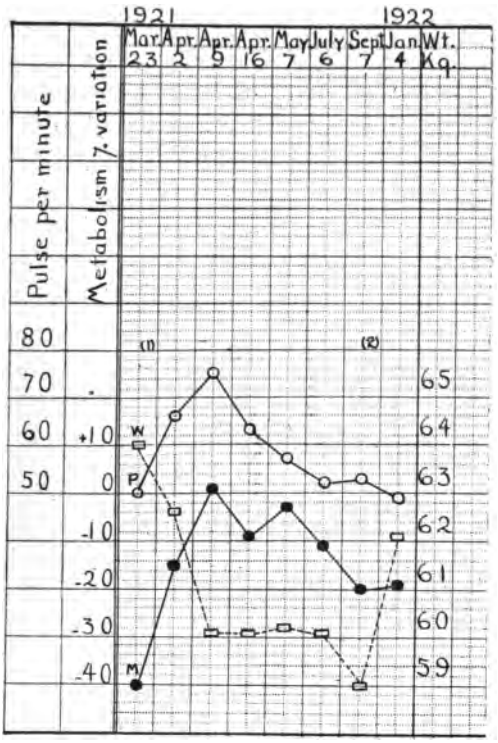

Fig. 240.—D. A. Mc. (M. 16,750). *P*, Pulse-rate; *M*, metabolic rate; *W*, weight in kilograms; (1) photograph taken (Fig. 238) before thyroid feeding; (2) photograph taken (Fig. 239) after thyroid feeding. Thyroid therapy was commenced on March 23d and was promptly followed by an increased metabolic rate, a rise in pulse-rate, and a loss of weight. The patient left the hospital on May 7th, and was then taking 0.26 gm. alternating with 0.13 gm. q. d. This dosage was apparently too small, as indicated by the continued fall in the metabolism and pulse-rate. The patient was then given 0.25 gm. alternating with 0.39 gm. q. d., which was probably the correct dosage, as his general condition continued to improve. Unfortunately, it is impossible to judge correctly from the determination on January 4th, as for six days prior to that time the patient had been away from home and had not taken thyroid tablets.

accurately just when the initial symptoms were noted. About five years ago he was an enterprising and ambitious worker in a brokerage office, occupying a position of considerable responsibility. At this time he developed a gradually increasing mental slowing and an impairment in his memory. This

soon became so apparent to his employers that he was shifted from a position of considerable importance to one which required but little ability. At this time the patient's general character seemed to change. He had formerly been very jovial and entertaining and a hard worker. With the onset of the present trouble he lost all interest in both the labor and entertainment of life and appeared to age markedly. Coincident with this his face became "bloated" and his friends remarked upon the change in his facial expression and color. Soon after the appearance of these symptoms he began to lose the hair of his scalp and eyebrows, and the hair over the arms and legs completely disappeared. His skin became very rough and dry and acquired a brownish tint. He observed that his appetite was usually very poor, and yet, in spite of his small food intake, there was no decrease in his body weight, as his average weight for the past ten years had been about 170 pounds. He suffered greatly from the cold during the fall and winter, and on account of this required an abnormal amount of bedclothes at night, and dressed very warmly during the day. On the other hand, he did not object to warm weather, and could not recall that he has perspired for several years, even when heavily clad and walking briskly during warm weather. In early life he was regarded as having a good voice, and was formerly a member of a glee club, but recently his voice became much deeper and acquired a harsh, coarse quality. His mental deterioration progressed until he was of no use to his employers, and consequently, about a year and a half before admission to this hospital, he lost his position. He gradually became incapable of performing even simple tasks efficiently, but continued to do light work on farms during the summer and odd jobs in the city during the other seasons.

Physical Examination.—The patient presented the characteristic appearance of myxedema, with an increase in the subcutaneous tissues of the face, particularly about the eyes, thin hair of the scalp and eyebrows, and thickened lips and nostrils (Fig. 241). The axillary and pubic hair was scanty and the hair of the arms and legs was absent. The skin was

rough, dry, and cold to the touch. The voice had a coarse, hoarse quality. There were moderate rounded elevations over both clavicles. The examination of the heart, lungs, and abdomen was negative. The patient's temperature (by mouth) reached as low as 95° F., and the lowest pulse-rate observed on the ward was 60 per minute.

Urine.—Sugar, 0. Albumin, 0. Sediment showed a rare leukocyte, otherwise negative. Phthalein test was 68 per cent. in two hours and ten minutes.

Fig. 241.—J. B. (M. 16,607). Moderately advanced myxedema before thyroid feeding.

Blood.—Red blood-cells 4,144,000. Hemoglobin (Sahli) 68 per cent. White blood-cells 9900. Differential count: Polymorphonuclears 59 per cent., lymphocytes 29 per cent., large mononuclears 9 per cent., eosinophils 3 per cent. The red blood-cells showed moderate achromia and slight variation in size and shape.

Basal metabolism on August 26th was 33 per cent. below the average normal.

Clinical Course.—The details of the course of the disease

as indicated by the body weight, basal metabolism, and pulse-rate are given in Fig. 243. Two days after treatment had been instituted with thyroid tablets, the temperature, which had previously ranged between 95° and 97° F., rose to between 97° and 99° F., and on one day reached 100° F. There was a corresponding increase in the pulse-rate from an average of about 70 to about 90 per minute. The patient had a feeling

Fig. 242.—J. B. (M. 16,697). The same patient as Fig. 241 after having taken thyroid tablets for four and a half months. Note the amazing growth of hair of the scalp, and the disappearance of the pigmentation from the face.

of warmth shortly after beginning the thyroid extract and perspired for the first time in several years. There was a rapid disappearance of his mental inertia as shown by the interest displayed in his surroundings and the desire to resume his former occupation. The recovery was complete, and for the past six months the patient has been occupying his former position and is apparently fulfilling his duties in a highly satisfactory manner.

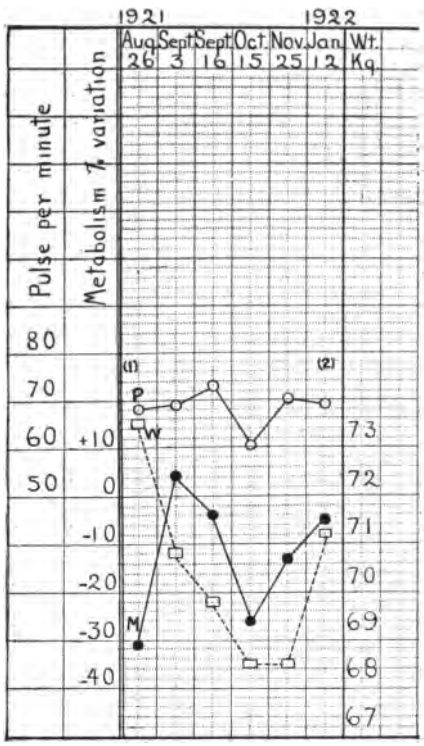

Fig. 243.—J. B. (M. 16,697). *P*, Resting pulse-rate per minute; *M*, metabolic rate; *W*, weight in kilograms; (1) indicates when the photograph shown in Fig. 241 was taken, before thyroid tablets had been given, and (2) is the date when the second photograph shown in Fig. 242 was taken, after four and a half months of thyroid therapy. Thyroid medication, 0.13 gm. t. i. d., was instituted immediately after the initial metabolism determination on August 26th, and this continued for six days, when the dose was reduced to 0.13 gm. b. d. The metabolism rapidly rose from 32 per cent. below normal to 4 per cent. above normal, and with this there was a loss of 2.7 kilos in weight. The patient was discharged from the hospital with a metabolism of 4 per cent. below normal, and instructed to take thyroid tablets 0.13 gm. q. d. for two successive days, and then omit one day. This dosage proved inadequate, as his metabolism in a month's time fell to 26 per cent. below normal. The thyroid dosage was increased on October 15th, with a resultant rise in metabolism to 5 per cent. below normal. The weight curve is quite characteristic, as it indicates an initial loss of 5 kilos following the administration of thyroid gland, but with a subsequent gain of 2.7 kilos as the general condition of the patient improved following treatment.

DISCUSSION OF TABLE I

The principal facts concerning the 15 patients with myxedema are recorded in Table I. It is seen that the disease in our experience has been more frequently encountered in females than males, there being 10 women in the 15 cases. This is in accord with the general view that the disease more frequently occurs in women than in men. Three of the most striking and characteristic pictures of the disease, however, were observed in men (Cases 9, 10 and 11). A consideration of the ages of these patients indicates that it is essentially a disease of middle age, which is likewise in agreement with the generally accepted view. That it may be present at almost any age is shown by its occurrence in one patient of twenty-two years (Case 2) and another of seventy-three years (Case 13). The latter patient is of considerable interest, as she was a highly intelligent woman, thoroughly conversant with all the phenomena of myxedema. She stated that over thirty years ago she developed a condition characterized by extreme weakness and after consulting many physicians, including several in France, was told that she had "nervous prostration" and advised to take a long rest. On returning to this country her true condition was recognized by a Boston physician, who administered a thyroid preparation.[1] The initial dosage was apparently excessive, as the patient relates that she lost a great deal of weight and became exceedingly nervous. Her condition became so

[1] This patient's statement, if accurate, indicates that she was among the earliest, if not the first in the United States, to be treated with thyroid gland by mouth. She asserted that the treatment was begun "in 1892 or 1893." The physician who advised this therapy was Dr. William Jackson, of Boston. It is recalled that Dr. George Murray read his paper "On the Treatment of Myxedema by the Hypodermic Injection of an Extract of the Thyroid Gland of the Sheep" at a meeting of the British Medical Association in July, 1891, and this was published in the British Medical Journal of October 10, 1891. About one year later (October 29, 1892) there appeared two papers in the British Medical Journal, one by Dr. Hector MacKenzie and the other by Dr. E. S. Fox, which reported the beneficial effects of feeding thyroid preparations to myxedema patients by mouth. It was hoped that this case, doubtless unique in its time, had been reported in one of the medical journals, but a search through the medical literature of the early '90's did not reveal a case report suggestive of this patient.

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alarming that it was necessary to send her to a hospital. Subsequently, with readjustment of the thyroid dosage, her condition steadily improved, and the treatment was continued with a highly satisfactory result until about three years ago, when the patient on her own responsibility gradually discontinued the use of the drug. She was influenced in this, as she thought it was the cause of "pain in the right shoulder-joint." After a lapse of several months the symptoms of myxedema again supervened and remained until admission to this hospital.

The most constant chief complaints of patients with this disease as illustrated by this series are weakness, swelling of the face or ankles, and chilly sensations. One patient (Case 4) was admitted with a complaint of "pain in the side, nausea, and vomiting," and she presented the typical picture of cholelithiasis which probably had no relation to her myxedema. The acute attack of pain, referable to the gall-bladder, terminated suddenly, and shortly after a large gall-stone was discovered in her stool. Her general appearance suggested myxedema, and further investigation readily confirmed this diagnosis. It is interesting to note that one other patient (Case 1) was admitted with a diagnosis of gall-stones, and gave a history of several sharp attacks of upper abdominal pain and a period of vague gastric symptoms extending over several years. Attention was directed toward the diagnosis of myxedema on account of a very rough and dry skin. It is not understood how the acute attack of pain could have any other than an incidental association with myxedema. Following thyroid therapy the patient made a complete recovery, and several years later was reported to be in perfect health. Other complications existed in a number of the patients in this series. Case 3 had an aortic insufficiency and later developed a carcinoma of the breast. After a year of thyroid therapy with marked improvement the patient got out of touch with the hospital and the drug was not given in sufficient amount. She returned after an interval to the hospital for observation of the breast condition and operation was subsequently advised. Following the operation the patient had a prolonged convalescence and the

wound healed very slowly. This illustrates a reaction quite typical of patients with myxedema, as it has been previously noted that they do not tolerate even minor operative procedures well.

In 10 of the 15 patients there was a record of the diagnosis prior to admission to this hospital, and in nine instances the true nature of the condition was not discovered, though often the patient had consulted a number of physicians who had failed to discriminate between myxedema and Bright's disease or "anemia." It cannot be too strongly emphasized that the diagnosis of this disease does not offer any great difficulty, provided the possibility of it occurs to the physician.

A glance at the table indicates the symptoms which are most frequently observed. The so-called solid edema, usually of the face, and most marked about the eyes, occurred in all of the patients but one, and in this instance there was no record stating whether it was or was not present. Ten of the patients presented characteristic mental changes, usually slowness of thought, lack of initiative, loss of memory, and inability to concentrate. In 2 of the patients there was no mention of mental changes, and in 3 the mental condition was said to be normal. All patients showed the characteristic changes in the skin, most frequently described as rough, dry and parchment-like, and often displaying a desquamation or scaling. Pigmentation of a yellowish or brownish tinge is likewise a very common finding. Though lack of perspiration is not mentioned in all of the histories of these patients, this symptom has been constant in all patients whom I have personally seen, and it appears to be highly characteristic of the disease. Alterations in the hair, though not always striking, were reported as present in 14 of the 15 patients of this group. There were no typical changes in the hair which occurred constantly. The loss of the outer third of the eyebrows, considered by some as common in this disease, was not present in some of the advanced cases. It is often difficult to state accurately whether or not the amount of hair in the axillæ, pubic region, and over the body is abnormally sparse. On the other hand, when the changes in the hair are

striking, as, for instance, the presence of a "border band of alopecia" or when there is an absence of hair over the entire body, it constitutes one of the most reliable signs of the disease.

The sensitiveness to cold, which is undoubtedly due in part, at least, to the low metabolism, probably occurs in all individuals with this disease, and there was a statement in the history that it was present in 10 of the 15 patients of this series. No note was made concerning its occurrence in the remaining 5 patients, but it seems logical to assume that it must have been present as a symptom, inasmuch as all of these patients had a lowered metabolism.

Patients with myxedema usually give a history of their weight remaining stationary or otherwise a gradual gain in weight of from 10 to 20 pounds during the course of their present illness. Seven of the patients in this series reported a moderate gain; 4 stated that their weight had remained stationary; and 3 gave a history of loss of weight, 1 a questionable amount, another 19 pounds in one year, and a third 17 pounds in six years. These patients do not, as is sometimes supposed, gain an enormous amount of weight. The amount gained as a result of their disease is represented by the amount lost when thyroid therapy is instituted, and this averages between 10 and 20 pounds. When one considers that these patients have an abnormally low metabolism, or energy requirement, and hence need but little food in order to maintain or even gain weight, it would naturally be expected that they would give a history of eating a rather small amount of food, yet not losing weight. In seven instances these patients considered their appetites poor or very small, in seven it was good, and in one it was not noted on the record. The combination, then, of a small appetite with maintenance or a gain of body weight may be present in myxedema, though it is not a constant feature.

The hearing in 7 of the patients of this series was impaired, 1 being totally deaf. In 7 there was no change noted, and in 1 there is no record of the hearing in the history. While some of these patients may have had an anatomic change as a basis

of their defect in hearing, it is perhaps in some respects due to inattention rather than actual changes in the ear.

Changes in the speech, either in the manner of speech or in the voice, are apparently very common in this disease, as peculiarities in either one or the other or both of these were reported in 14 out of the 15 patients. The mode of speech in these patients was usually characteristically described as slow, hesitating, thick, monotonous, and deliberate. The voice itself becomes altered and often has a coarse, husky, harsh character. The cause of these changes is referable to

Fig. 244.—M. J. B. (M. 4197). Patient with severe myxedema associated with advanced nephritis.

the mental retardation and the thickening of the tongue and vocal cords.

A study of the urine and the renal function is of special interest, as the diagnosis in these patients has so frequently been confused with nephritis. Examination of the urine in the 15 patients showed the presence of albumin in 7, and this was usually associated with a few hyaline casts. Two patients who did not show the presence of albumin in their urine did have a few granular and hyaline casts present. In 5 patients the urine examination, which in all but one instance included

the study of several twenty-four-hour amounts, was entirely negative. In 12 of these patients the phthalein excretion was determined according to the usual technic, and in all but two instances it was found to be entirely normal. In one patient (Case 8) there was evidence of an advanced nephritis as indicated by a phthalein excretion of 8 per cent., and the presence of albumin, granular casts, white blood-cells, and red blood-cells in the urine. This patient was given thyroid tablets and the symptoms of myxedema rapidly disappeared. Her appear-

Fig. 245.—M. J. B. (M. 4197). The same patient as shown in Fig. 244 after several months of thyroid therapy.

ance underwent a remarkable transformation, as illustrated by the accompanying photographs (Figs. 244 and 245), yet the patient died several months later, apparently of renal insufficiency. A second patient (Case 13) showed the evidence of a moderate nephritis, which at the age of seventy-three might be interpreted as a part of a generalized arteriosclerosis.

The temperatures recorded in Table I were taken by mouth, with one exception, at the time of the metabolism determination, and it is seen that in each instance it was subnormal, though the depression was only very slight in a number of patients.

In the majority of these patients the temperature when taken on the ward at four hourly intervals was found to be constantly subnormal, most frequently varying between 96° and 97° F. by mouth.

The pulse, when taken after a minimum of thirty minutes' rest in bed, was in most instances slow. Twelve patients had a resting pulse between 50 and 70, while the highest pulse recorded was 80 per minute. These pulse-rates are not lower than one frequently observes in normal people, but this tendency to a bradycardia is significant from a diagnostic standpoint, as a rapid resting pulse is not commonly observed in myxedema. When a tachycardia is encountered in a patient who is suspected of having the disease it throws some doubt upon the diagnosis.

The blood-pressure readings indicate a tendency to hypotension in this disease. This is manifested most markedly in Cases 6, 8, 9, 10, and 15. The remaining 10 patients had readings which may be considered normal or slightly below normal.

The striking constancy of the effect of feeding thyroid tablets is well illustrated in these 15 patients. In 14 instances there was either a complete cure or a marked improvement following the use of this drug. It has not been possible to follow all of these patients, but in most instances they have reported to the hospital at intervals for observation. A number have shown remarkable improvement during their stay in the hospital of several weeks, but they have not returned for observation and have not replied to follow-up letters. One patient (Case 8) is known to have died a few months after leaving the hospital, probably as a result of a complicating renal lesion. Another patient (Case 12) refused to take thyroid tablets, as she believed they would cause a recurrence of diarrhea, which she previously had and probably wrongly attributed to the medication. A third patient (Case 13) took thyroid extract intermittently, and while the improvement was not the maximum, she was greatly benefited.

THE BASAL METABOLISM IN MYXEDEMA[1]

Whatever other functions may be attributed to the thyroid gland it is safe to say that it exerts a definite and profound influence on heat production in the body, and this, when measured, constitutes the most reliable index of the functional activity of the gland. In myxedema, or hypothyroidism, the most characteristic finding is a low metabolic rate, and it has never been our experience at this hospital to see a patient in whom it is possible to make a clinical diagnosis of myxedema who has not had this alteration in the basal metabolism. There is evidence to indicate, as Plummer[1] has emphasized, that at least one of the prominent symptoms of the disease, the edema of myxedema, becomes recognizable only when the basal metabolism drops from 15 to 17 per cent. below the average normal. It seems, therefore, that a fall in metabolism is the earliest change associated with diminished function of the thyroid gland.

On the other hand, a low metabolism when considered alone does not always mean that a patient has myxedema, for such a change may be observed in association with various other conditions, which, from a clinical standpoint, do not resemble myxedema in the slightest. Hence the result of a basal metabolism determination, in this disease as in any other, should be interpreted only after the fullest consideration of the clinical aspects of the case. A metabolic rate which averages 20 per cent., and may be as much as 30 per cent. below normal, is

[1] All basal metabolism determinations were made following a fourteen-hour fast and after the patient had been lying in bed for at least one-half hour. The expired air was collected by means of a face mask, which covered both the nose and mouth, and which was connected with a 100-liter modified Tissot spirometer. Analysis of the expired air was done with the portable Haldane gas analysis apparatus. The heat production in calories per square meter per hour was then calculated from the oxygen consumption and the calorific value of oxygen as determined by the respiratory quotient. The results were compared to the standards of Du Bois and expressed in percentage of normal. The expired air was collected for two nine-minute periods. For the past two years a separate set of valves, spirometer, and face mask has been used for each period. In all but very rare instances the two results thus obtained have checked within 5 per cent.

found quite regularly in patients with hypopituitarism. Under nutrition may likewise be a factor in causation of a low basal metabolism, as Benedict[8] and his collaborators have reported, and we have assumed this as a logical cause in a number of patients who have had a basal metabolism below normal limits, and for which there was no other obvious explanation. The following single instance will suffice as an illustration: An emaciated, neurasthenic girl of sixteen, whose appetite had been exceedingly small for a period of several months, was found to have a basal metabolism of 20 per cent. below normal. As she did not otherwise have the slightest indication of myxedema or hypopituitarism, it was doubtless correct to assume that undernutrition was responsible for the abnormality in the basal metabolism. The effect of undernutrition was clearly illustrated in another instance in this hospital, wherein a patient with epilepsy underwent a complete fast of three weeks as a curative measure. At the end of this period there was a drop in the basal metabolism to 44 per cent. below normal.

One source of error relative to the interpretation of the basal metabolism determination should be emphasized, and this is the tendency of clinicians to attach too much significance to minor variations from normal. While we have found the normal standards of basal metabolism, as established by DuBois, to be as satisfactory as the standards of any procedure used in medicine, yet it is too much to expect that they will invariably express the precise basal metabolism of every individual. Hence, a slightly diminished basal metabolism in some individuals may be due to a normal variation from the accepted standards, and unless the patient displays some definite clinical manifestation of myxedema the result should be ignored. An instance of this was encountered in a healthy, apparently normal house officer of this hospital whose basal metabolism was determined during the course of some experimental work for which he had volunteered as a subject. His basal metabolism was found to be between 22 and 25 per cent. below normal on three occasions over a period of several months. If this instance is one of a normal individual with a basal metabolism con-

siderably below the accepted standards, it is an unusually large variation and one rarely encountered.

It has been noted, furthermore, that the basal metabolism in a series of normal individuals, all house officers or medical students, in many instances tended toward the extreme lower border of normal; that is, between 10 and 16 per cent. below the normal average. It may be that these individuals, in an endeavor to co-operate, attain almost complete relaxation which is similar to that observed during sleep, and this might well account for the slightly diminished, but not abnormal, metabolism.

It is interesting to note that many of the symptoms of myxedema are referable, at least in part, directly or indirectly to the low basal metabolism or heat production. It is easy to understand why an individual, who is radiating 30 to 40 per cent. less heat than normal, should complain of chilliness, and have a subnormal temperature, and a skin which is cold to the touch. Furthermore, as a patient with a low metabolism has little if any excess heat to radiate, it is logical to assume that this is one factor which accounts for the absence of perspiration, which is characteristic of patients with myxedema. The bradycardia, often observed in myxedema, is probably associated with the decreased metabolism, for when such a condition exists in the body the cells utilize less oxygen and produce a smaller amount of carbon dioxid. Under these circumstances a diminished blood flow is adequate to convey these gases between the tissues and the lungs, and if it is assumed that the rate of the heart is a fair criterion of its output, then bradycardia is to be expected. The low metabolism likewise is responsible for the small amount of food which these patients consume, and enables them, despite this, to maintain their body weight. In some instances they may gain, but this is often due, however, to the accumulation of solid edema. If an apparatus for determining the basal metabolism is not available, a consideration of these symptoms, which are directly associated with a low metabolism, is often helpful in deciding whether or not the metabolism is below normal.

The basal metabolism studies in this group of 15 patients are shown in Table I, and it is seen that the results vary from 49 to 24 per cent. below normal. In 11 of these 15 patients, however, the results were 30 per cent. or more below normal. The average depression in the metabolic rate of the entire group is 33 per cent. below normal. Hence the diminution of the basal metabolism in myxedema is usually greater than that observed in other diseases; therefore when the basal metabolism of a patient is found to be 30 per cent. or more below normal it is almost always due to underactivity of the thyroid gland.

THE DIAGNOSIS OF MYXEDEMA

Without a determination of the basal metabolism the exact diagnosis of myxedema may be exceedingly difficult, but the symptoms and signs which are suggestive of this condition are quite definite and striking. The history, as given by the patient, is often rambling, illogic, contradictory, and frequently is of little assistance, unless one suspects, when taking the history, that the patient has myxedema. It is then possible, without asking leading questions, to obtain a great deal of information which is helpful in eliminating or establishing the diagnosis. If the patient's complaints include loss of energy, inability to perform mental tasks efficiently, chilliness or sensitiveness to cold, or it is observed that the patient has a full rounded face with puffiness under the eyes, marked loss of hair, subnormal temperature or bradycardia, then the diagnosis of myxedema should be considered and further investigation conducted accordingly.

The conditions most frequently confused with myxedema from the standpoint of diagnosis are pernicious anemia and nephritis. It is true that superficially they may resemble this disease in certain features. There are instances when the differential diagnosis of myxedema from these diseases is difficult without the aid of modern laboratory facilities, but ordinarily it should be easily accomplished.

The clinical picture of pernicious anemia has some characteristics, both subjective and objective, which are similar

to those present in the advanced stages of myxedema. The chief complaint in the two diseases is most frequently weakness, lack of energy, or ease of fatigue. There is often a brownish or yellowish tint to the skin in myxedema which suggest the color seen in pernicious anemia, though this color is not apparent in the conjunctivæ as in the latter disease. This combination of slight pigmentation with apparent good general nutrition is, then, common to both diseases. Sensitiveness to cold may be a complaint in either condition. Furthermore, about half of the patients with myxedema show changes in the blood-picture which are, however, usually of the nature of a mild secondary, rather than a primary, anemia. It occasionally happens that a patient with myxedema may have a reduction in the number of red blood-cells as low as 2,000,000, but even in these patients the blood-smear is not usually typical of a primary anemia, though it may resemble it somewhat. Patients with pernicious anemia may have a subnormal temperature, and it has been observed that the basal metabolism may be, in rare instances, as low as 20 per cent. below normal. There is no evidence at present which indicates that this reduction in metabolism, when present, is ever as great as the average diminution found in myxedema. The mental changes, the alterations in the skin and hair, the absence of sweating, while almost always present in myxedema, are not present in pernicious anemia. As it has been emphasized by Ladd and Levine[2] that the absence of free hydrochloric acid in the fasting stomach contents is found with great regularity in patients with pernicious anemia, it is of interest to consider the results of gastric analysis which was performed in 5 patients of this series. Three showed no free hydrochloric acid in the fasting contents and a low total acidity following the test meal, one showed a normal amount of hydrochloric acid both in the fasting contents and following the test meal, and one had a hypo-acidity in the fasting contents and following the test meal. These results, then, indicate that there may or may not be an absence of free hydrochloric acid in the fasting contents. Hydrochloric acid when present is good evidence against a diagnosis of perni-

cious anemia, but when it is absent this fact is of much less importance.

As these patients usually have swelling of the face and often of the ankles, and frequently show a slight trace of albumin and a few casts in the urine, they have many times been regarded as having nephritis. Such a diagnosis often bespeaks of a most casual and superficial examination on the part of the physician responsible for it. Though there may be a slight trace of albumin present in the urine, the cellular elements found in the urinary sediment are not of the type usually observed in advanced nephritis. The blood-pressure is either normal or subnormal rather than elevated, and the swelling of the face and ankles, as it is not due to the presence of fluid in the subcutaneous tissues, does not pit on pressure. Furthermore, the characteristic changes of myxedema in the skin and its appendages are not seen in disease of the kidneys. It is possible that a true nephritis may be associated with myxedema, but when it is present, the urine examination shows the characteristic picture of nephritis and the phthalein test further indicates a decreased renal function. Nephritis, when present in myxedema, is regarded as an incidental association, according to the generally accepted view at present.

In some patients with myxedema there may be marked brownish pigmentation of the skin, and when this is combined with a reduction in the number of red blood-cells, hypotension, and a chief complaint of marked asthenia, it suggests the diagnosis of Addison's disease. The other characteristics of myxedema, however, as the good general nutrition, changes in the skin and hair, and the absence of gastro-intestinal symptoms, usually suffice to make the differentiation easy.

A patient with neurasthenic symptoms may simulate in some respects a mild type of myxedema, as their most prominent complaint is ease of fatigue. They may also have other symptoms of myxedema, as sensitiveness of cold, and a real or fancied loss of memory. When these neurasthenic symptoms follow the natural or artificial menopause and the patient has gained weight the resemblance to myxedema is more marked.

There are no other characteristic features of hypothyroidism present in these patients, and metabolism studies, if available, readily separate the two conditions.

THE TREATMENT OF MYXEDEMA

The administration of tablets of dried thyroid gland promises immediate and prompt relief to all patients with myxedema provided the proper dosage is used and there are no complications, as, for instance, an advanced chronic nephritis or marked mental changes. The required dosage varies in different patients, and hence the best method is to administer as an initial dose a moderate amount, such as 0.13 gm. three times a day for a period of several days. At the end of this time there will be a loss of several pounds in weight, the temperature will rise from subnormal to normal, or there may be even a degree or so of fever, as happened in several of the patients at this hospital. At this time the metabolism should be determined as a guide to further therapy, and it is usually found to be approximately normal. If the metabolism is normal the thyroid medication should then be reduced to a maintenance dose; that is, the smallest amount that will keep the metabolism and pulse at normal levels. The size of this dose is variable in different individuals, but an average amount in a patient with complete myxedema is 0.13 gm. twice a day. Some of the patients of this series require only 0.13 gm. a day as a maintenance dose, while others use as much as 0.13 gm. three times a day.

The same guiding principles should be used in thyroid gland therapy as the one frequently followed when giving digitalis to cardiac patients; that is, a preparation known to be potent should be administered in moderate doses until either a beneficial effect is produced or early and very mild symptoms of overdosage are noted. In treating myxedema it is unnecessary to push the drug until toxic symptoms are produced if the facilities for doing the basal metabolism are at hand, for the dosage may be reduced as soon as the metabolism reaches normal. If the amount of the drug is reduced at this time the symptoms of overdosage are averted.

If the ingestion of an appropriate amount of thyroid tablets is not followed by changes, either in the basal metabolic rate or the general condition of the patient, then the dose should be cautiously increased and the patient closely observed for the appearance of mild toxic symptoms, as palpitation, flushing, or an excessive feeling of warmth. It occasionally happens that the dosage may be raised to a very large amount and yet no effects are apparent. Under these circumstances the failure of the drug to act may be due to one of two reasons: either the thyroid preparation is inactive or it is not absorbed from the alimentary tract. The first condition rarely occurs, as most of the thyroid tablets prepared by reliable drug firms are satisfactory. The latter explanation has been the most logical one to account for the occasional failure to obtain results following the administration of large amounts of the drug. The failure of the alimentary tract to absorb thyroid gland tablets is important, for when the drug is given as a therapeutic test and no improvement follows it may be that none is absorbed. If after a thorough and careful trial no results are obtained, it is wise to resort to a different preparation of thyroid tablets, or to use thyroxin by mouth as it is now manufactured by one of the large drug firms and is available to the profession. Other factors may also complicate the picture when expected results do not follow thyroid therapy. This is illustrated by M. F. (Med. 17,180), a woman aged fifty-two, who had symptoms of myxedema extending over a period of fifteen years. She had the characteristic history and appearance of a patient with myxedema, and her basal metabolism was found to be 25 per cent. below normal. She stated that dried thyroid gland had been given her some years before, but it was not tolerated well, inasmuch as it always caused diarrhea. As it was essential that she should be given thyroid tablets, it was administered in moderate doses in capsules. The patient was not told the nature of the drug and it was hoped that the capsules would disguise it sufficiently. During a period of several weeks this therapy was continued, but neither diarrhea nor changes in the metabolism, pulse-rate, nor body weight followed. As she in-

sisted on leaving the hospital, she was discharged, unimproved, and ordered to continue the capsules and report to the Outdoor Department for further observation. It was later learned from the patient's physician that she had suspected the capsules contained thyroid gland, and after confirming this by opening and tasting the first one given her, she had succeeded each time thereafter in deceiving the nurse, with the result that she had not taken one single dose of the drug during her stay in the hospital. In another instance a patient was advised to take thyroid tablets to relieve the myxedema which had developed during the course of the Roentgen-ray treatment of hyperthyroidism. She refused to take the drug regularly, as her physician had previously given her thyroid tablets at the time she had hyperthyroidism, and there followed an intensification of her symptoms with a resultant abnormal fear of the drug which caused her to believe that it could not be taken with safety under any circumstances.

Two other patients of this series, on their own initiative, discontinued the use of the thyroid tablets, and each one in the course of six to eight weeks again developed the symptoms of myxedema. In one instance the patient stopped the drug "because she felt so well," and in the other it was discontinued because she insisted that the "medicine caused a pain in the shoulder-joint," an association which was, no doubt, only an incidental one.

All patients when first given thyroid tablets should be under rather close supervision by a physician. It is advisable, if the disease is at all advanced, to confine them to bed for several weeks, until the striking changes in the metabolism are concluded, as at this time there might be slight fever, nausea, and other mild symptoms. In the less advanced cases this is unnecessary, but a patient should, at least, be seen once a day until the metabolism and pulse are normal, and then at less frequent intervals until it is apparent that the smaller doses prescribed are sufficient to maintain the normal conditions. It has been our experience that once a maintenance dose is established it continues to be fairly constant, though some

patients seem to require a slightly larger dose during cold weather. It is also our impression that some patients feel better when the metabolic rate is at the lower level or normal according to the standards of Du Bois; that is, between 5 and 10 per cent. below the average normal. Under these circumstances the general condition of the patient, the pulse, and the weight curve are of assistance, when taken in conjunction with the metabolic rate, in deciding the exact thyroid dosage.

Excessive thyroid medication may produce disagreeable and even dangerous symptoms, but they are easily avoided if the patient is closely watched. As illustrations of improper thyroid medication the following 2 cases serve as examples:

J. F. K., a business man, fifty years of age, was admitted, complaining of swelling of the ankles and puffiness of the eyelids. He was found to have myxedema, and on discharge from the hospital was instructed to take thyroid tablets 0.13 gm. twice a day. His basal metabolism before treatment was 25 per cent. below the average normal. After sixteen days of treatment he felt much improved, and by this time there had been an increase in the basal metabolism to 5 per cent. below normal. There had also been a loss of 3.4 kilograms in body weight, and the resting pulse-rate had increased from 58 to 63 per minute. As satisfactory changes had thus far resulted, he should have been advised at this time to take a smaller dose per day, in an endeavor to maintain the normal level of metabolism which had been reached. Instead, he was permitted to continue taking the same dose of 0.13 gm. twice a day for a period of forty-two days. Though it is not recorded that he experienced any of the usual symptoms of overdosage, there was an increase in the basal metabolism to 39 per cent. above normal. There had also been a loss of 7.7 kilos in body weight, and the resting pulse-rate had increased to 85 per minute. In view of this obvious evidence of excessive dosage the drug was, of course, discontinued, but over an undue length of time, for when the patient returned after an interval of forty-three days, during which time he had not received any thyroid preparation, the symptoms of myxedema were again apparent and the

basal metabolism had fallen to 24 per cent. below normal. The patient had gained 5.1 kilograms in body weight in this period and the resting pulse-rate had decreased to 59 per minute. The errors in the treatment of this patient were, then, the continuance of an excessive dosage after the patient's metabolism had increased to normal limits (5 per cent. below normal), and the withdrawal of the drug for such a long interval that many of the symptoms and signs of myxedema recurred. This emphasizes clearly that the administration of thyroid gland, though regarded by many as a simple matter, requires a certain amount of care and judgment in order to obtain successful results.

A second patient had an experience somewhat similar to the one recorded above. G. L. F., age twenty-two, a stenographer, was admitted to the hospital complaining of weakness and swelling of the face. She gave a characteristic history of myxedema extending over a period of eighteen months. Her basal metabolism was 34 per cent. below normal. She remained in the hospital thirteen days and during this time received 0.13 gm. of thyroid gland tablets three times a day. After leaving the hospital she continued taking this amount of the drug for an additional four days. She then developed marked weakness, nausea, vomiting, nervousness, and insomnia. Associated with this there was a loss of appetite and a decrease of about 19 pounds in body weight. Nineteen days after the medication had been discontinued she returned to the hospital to have her metabolism determined, and it was found to be 22 per cent. below normal. Subsequently the dosage was adjusted to 0.13 gm. a day, and she has continued to take this amount almost continuously for three years with excellent results. The manifestations displayed by this patient as a result of the ingestion of an excessive amount of thyroid gland are quite typical.

The earliest symptoms of overdosage consist of a sensation of excessive warmth, palpitation, headache, dizziness, and slight tachycardia. If the drug is discontinued for a few days and then commenced in smaller doses, these symptoms rapidly

disappear. If, however, the excessive dosage is continued, vomiting, marked tachycardia, severe diarrhea, fibrillary tremor, and insomnia occur, and, finally, collapse may supervene.

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CLINIC OF DR. BRONSON CROTHERS

CHILDREN'S HOSPITAL

THE EFFECT OF BREECH EXTRACTION UPON THE CENTRAL NERVOUS SYSTEM OF THE FETUS

IN a neurologic clinic we see the end-results of the accidents at childbirth. One of the chief functions of such a clinic is the direction of these unfortunate children to the institutions for the crippled and the feeble-minded. On the other hand, it has a far more interesting function, which is less generally recognized, as a place of judgment on obstetric technic. It is that aspect of its work that will form the basis of this discussion and not the relatively depressing patients we have here.

I wish to discuss the technic of breech extraction in its broadest interpretation, meaning by it any operation involving traction on the legs or body of the baby. Naturally, I am not competent to discuss details, but I do believe that it is not impertinent, in a neurologic clinic, to consider etiology of neurologic lesions, and in birth injuries the etiology of the disease and the delivery of the child appear to be coincident.

In the first place, the clinical evidence that breech extraction and spinal injuries stand in the relation of cause and effect is as follows: Seven cases of spinal injury at birth, seen in this clinic and in private practice within two years, followed extraction. I have never seen such lesions after birth head first, nor have I been able to find any reports in the literature except after extractions.

In the second place, there is abundant pathologic evidence, gathered from all parts of the world, which suggests that injuries of the spinal column are common in extractions and almost unknown in other procedures. One contribution which,

as far as I know, has escaped general attention is that of Stoltzenburg. It is worth considering in some detail.

This observer found, in 9 cases, gross damage to the vertebral column out of 75 babies dying of "asphyxia." Eight of these followed extraction. She states that in every case the fetal heart left nothing to be desired at the beginning of extraction, every baby was born with its heart still beating, and none could be induced to take a spontaneous breath. The autopsy findings were very uniform. The cord showed no gross injury. The spinal column was torn, the intervertebral ligaments ripped, and there was profuse hemorrhage into and about the vertebral canal, covering the upper cord and medulla with clots. In addition, one case showed tears in the tentorium.

Stoltzenburg then demonstrated that identical injuries could be produced by traction and lateral flexion without employing any force beyond that usually exerted in delivery. One point, which may be of interest, is the observation that each of these babies had an extended arm which caused some difficulty in delivery.

These statistics and various others, less striking, are of importance only as they demonstrate that spinal injuries are common everywhere. Obviously, individual skill and restraint may make them rare in the practice of any one group of operators.

A careful search of all available recent obstetric text-books in English, French, and German resulted in no useful information whatsoever. Readers are furnished with a very detailed discussion on asphyxia and instructed in methods of rapid extraction, but nowhere is there the slightest warning against the danger of injuring the neck of the baby by any legitimate use of traction. I get the impression that broken necks are regarded as unfortunate and discreditable accidents, about which the less said the better.

Anatomic text-books are little better, as they contain scanty information about the spinal column of babies.

A very brief consideration of breech extraction, as it is described in books, shows that it is a unique procedure in obstetrics, in that an entirely unphysiologic force is applied to a

structure which normally is not subjected to any comparable strain. As far as I know no other obstetric maneuver, used to deliver living babies, is so illogical or so potentially disastrous.

The application of traction to the spine results in lengthening a structure which, normally, is subjected to compression. Before accepting the idea that such a procedure is reasonable it seems proper to see what happens. Clinically, a vast number of babies die following its application and an appreciable number live as cripples as a result of it. Pathologically, it seems probable that adequate study would reveal injuries in a very large proportion of babies. Stoltzenburg found that over 10 per cent. of all babies dying in the Halle Clinic had broken necks as a result of the traction employed in breech delivery. The repeated assertion of obstetricians that if traction were not employed many babies would die anyhow of asphyxia is open to some question. The facts certainly suggest, to me, that most of the breech babies now born dead are killed by injury or by pressure, rather than by asphyxia. In any case it seems reasonable to study breech extraction from every possible point of view.

I take it that nobody questions that breech extraction is a purely mechanical problem. Therefore a consideration of the forces used and the materials employed seems fundamental. In reputable practice the external forces used appear to vary from practically nothing to the combined pull and push of at least two men. The materials which must resist this pull and push are the elastic fetal spine and the soft fetal head. In the absence of information in text-books I tried to find out a few essential facts about what happened to the baby when such variable forces were concentrated upon it.

The spinal column of the full-term fetus is a collection of elastic cartilaginous rings held together by rather brittle and inelastic bands of connective tissue. If an intact fetal cadaver is taken between the hands and subjected to alternate compression and extension, the spinal column varies in length about 2 inches.

I have here a baby with its spinal column exposed from the

front. It is clear that the very moderate force I can exert by compressing the spine between my hands flattens out the bodies of the vertebræ as well as bringing them together.

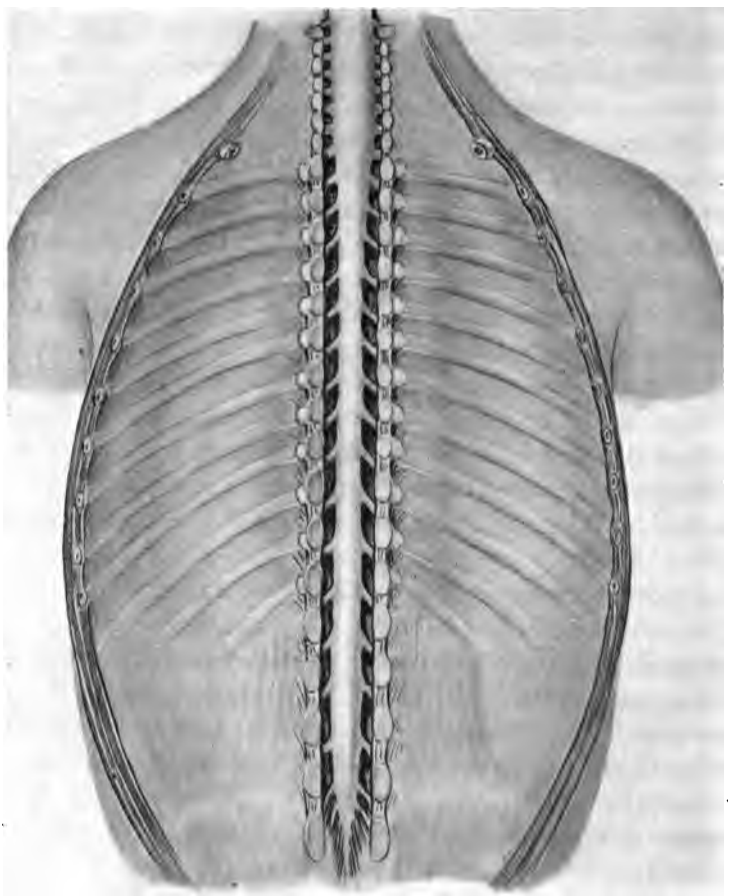

Fig. 246.—Dura of full-term fetus exposed from the front.

If I now extend the spine the vertebræ are separated at each joint and, in addition, stretch appreciably. Lateral bending, while the spine is under tension, causes yielding and tearing of the intervertebral ligaments at the point of bending. With a pair of scissors the bodies are now removed. You notice that this procedure is easy and involves no cutting of bone at all.

The dura is now exposed. The relations are obviously not exactly those seen in the adult. The upper cervical dura is firmly adherent to the edges of the foramen magnum, as in the adult, but it is also tied to the upper cervical vertebræ by strong fibrous strands. The cervical roots are short and practically horizontal.

When we go down to the thoracic region it is clear that the dura is a slender tube lying free, except as it is supported by almost filamentous roots with their fibrous sheaths. The lower end of the dural sac is firmly anchored by the strong lumbar and sacral roots and by fibrous bands attaching the dura to the sacrum and coccyx.

Traction pulls the cervical enlargement down about $\frac{1}{4}$ inch. Then the horizontal bands become taut. The lumbar enlargement hardly budges. The slender thoracic portion takes up the rest of the strain.

The cord is now exposed by slitting the dura. The cord is, as you see, a slender, fragile affair about $\frac{1}{8}$ inch in diameter, ending at the second lumbar vertebra. It is subjected to the same strains as the column and the dura.

From this rapid survey several facts stand out. The forces that are frequently exerted in delivery have been shown to be sufficient to rupture any or all the structures we have seen.

The gross vertebral ruptures cause death.

Traction alone puts a tremendous strain on the almost unsupported thoracic cord, and clinically, I have seen cases which must have had injuries due to this cause.

If an arm is extended it is easy to see that the lower cervical roots are put on the stretch. Again, clinical cases are available to indicate that avulsion of these roots is possible.

So much for the mechanism by which injuries of the spinal column and the cord are produced.

Another force, exerted with little restraint, is suprapubic pressure. In order to interpret on a physiologic basis the intracranial results of this force it is necessary to consider certain researches on intracranial pressure.

Any conception of the brain as a semifluid mass lying free

in a single cavity is totally inadequate. If the brain transmitted forces as a fluid nothing could prevent immediate and disastrous impaction of the medulla into the vertebral canal as soon as serious pressure was exerted. Very obviously this does not always happen. Repeated and accurate physiologic studies have made clear the points about intracranial and intraspinal pressures and their distribution, which are of importance

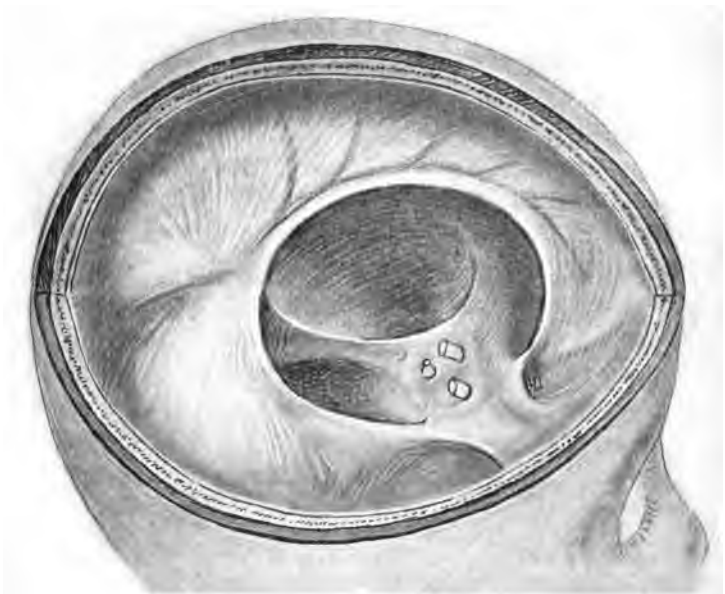

Fig. 247.—Dissection to show falx and tentorium. Before removal of the brain the tentorium is held down by the cerebral hemispheres and the cleft is much smaller.

in studying the effects of obstetric maneuvers on the nervous system of the fetus.

Observations by Hill, Cushing, Wolbach, and others have demonstrated beyond question that pressure is not transmitted equally in every direction. The brain tissue itself is viscous and putty-like and, by its own resistance, limits the spread of pressure. As compression increases its force is transmitted until it reaches the cranial walls or one of the great dural septa.

The structure and relations of the dural septa are, therefore, of interest.

I have here a dissection showing the falx and the tentorium in place. As a matter of fact, the tentorium is a little lower, in life, as the cerebral hemispheres hold it down, as can be shown in frozen sections. Furthermore, the opening for the midbrain and crura is smaller. However, the general structure and relations appear clearly.

The falx extends, as a sweeping crescentic membrane, from the crista galli of the ethmoid to its insertion in the midline of the tentorium. The falx thus divides, more or less completely, one side of the upper cranial cavity from the other. Along its upper border it splits to enclose the large superior longitudinal sinus, its free edge is occupied by the inferior longitudinal sinus, while the insertion into the tentorium encloses the straight sinus.

The tentorium is an arched dural fold separating the posterior and lower portion of the cranial cavity from the upper. Its origin along the sides of the skull surrounds the lateral and superior petrosal sinuses, while its insertion is into the clinoid processes. It is pierced by an opening just big enough to allow passage of the midbrain and crura.

Both the falx and the tentorium are very delicate membranes in the infant, but they are strengthened by strong curving strands of connective tissue so that they can resist great pressure without appreciable stretching.

In considering the distribution of pressure and its effect one other anatomic relation must be considered. The medulla and cerebellum lie just above the foramen magnum. Under conditions of rapidly produced intracranial tension they are forced down and completely close this opening.

The result is that three almost completely distinct pressure chambers are to be considered when serious force is applied to the soft vertex of the fetal skull. The situation can be represented graphically.

In addition to the direct force imposed upon the vertex there is a secondary force in the rise of blood-pressure which

always follows. This affects the subtentorial contents and raises pressure there. It also presumably, directly raises the pressure in the spinal compartment. Obviously any further movement is blocked as long as the tentorium holds and the spinal compartment is constant in size, as the part of the spinal canal not filled by the cord is occupied by incompressible fluid. Cushing showed that by increasing the spinal pressure he could prevent serious signs of compression, even though supratentorial pressure was raised to a considerable extent.

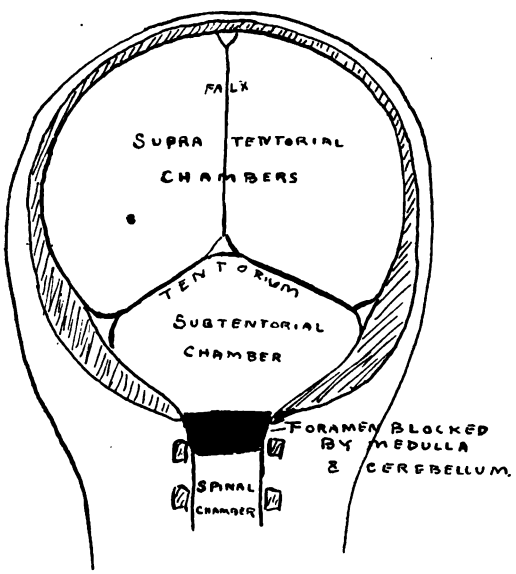

Fig. 248.—Coronal section behind the posterior margin of the corpus callosum to illustrate pressure chambers.

An important consideration now comes in. If all parts of the brain are considered as equally important to life, it is hard to follow the course of events in delivery.

As a matter of fact, the situation can be shown by studying various types of laboratory preparations.

This cat has been rapidly and rather crudely mutilated by complete removal of the whole of both cerebral hemispheres by section at the midbrain. This animal will live for hours

and will exhibit constant reflex phenomena and maintain its circulation without any artificial help. The cerebellum could be removed by section of its various peduncles. Reflex activities would be altered, but life would be kept up.

A very trifling accident involving the medulla will, however, kill the animal by blocking respiration and producing vasomotor collapse. Such a slight thing as the formation of blood-clot in front of the medulla may be all that is necessary.

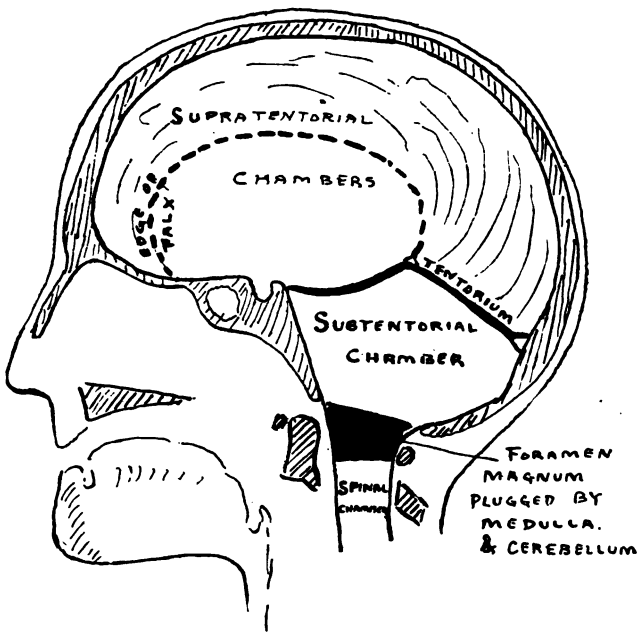

Fig. 249.—Sagittal section to illustrate formation of isolated chambers under pressure conditions.

Study of such a preparation suggests that the medulla alone is essential for unassisted prolonged life.

This second cat has been prepared by tracheotomy and the connection of an apparatus for rhythmic insufflation of air. By appropriate ligatures the cerebral arteries were secured. The animal was then decapitated. For a few minutes the cat remained flaccid. After this preliminary period of spinal shock

the animal began to respond to stimulation. It now shows flexion on pricking the foot and various other reflexes.

I will now disconnect the artificial respiration apparatus. The cat no longer receives air. The heart is beating. It does not and will not attempt to breathe. After a few minutes it will die as a result, I suppose, of a process which may be called asphyxia, though it is quite obvious that it is in as good air as the rest of us. Its death is due not to absence of surrounding air, but to absence of an excitable medulla. The analogy to certain obstetric conditions seems obvious.

It seems clear that, as long as fetal circulation is kept up, the baby, as a spinal mechanism, can be born alive without any activity of the brain whatsoever. It can breathe and obtain nourishment without anything but the medulla and cord. Observation of young babies does not contradict the theoretical conclusion that very little else is ordinarily used for weeks.

Whether the baby lives or dies, then, depends primarily on whether, at delivery, it has or has not an excitable medulla. Injuries or other lesions elsewhere in the nervous system do not matter in the least.

In normal labor, during pains, the head and the buttocks are simultaneously compressed. The spinal column shortens, the spinal pressure rises, and the medulla, though subjected to pressure, is guarded from trauma. It seems probable that normal labor, if at all difficult, will result in intracranial tension sufficient to put the central nervous system practically out of action, by anemia, during pains, without causing organic damage, while the intervals will allow re-establishment of circulation in at least the spinal and medullary portions.

In spontaneous breech deliveries exactly the same equilibrium of spinal and subtentorial pressures will exist until the breech is born. Then a sudden release of the spinal pressure occurs. The next pain may easily force the medulla further down. If this happens suddenly, a collapse of the baby may follow.

The great danger to the baby in breech extraction, I believe, lies in action based on serious misinterpretation of the signs. Both clinically and theoretically the critical stage for the baby

begins when the head reaches the pelvic brim and the breech is past the vulva. Obstetric text-books suggest, if they do not definitely state, that the fetal circulation is now inevitably shut off, and that, unless delivery is effected within eight minutes, the baby will die of asphyxia.

The obvious result is that a tensely expectant operator waits a little while and then extracts the baby at all costs. Everything is said to depend on the avoidance of asphyxia. The conventional exposition of the sequence of events is always the same. It runs essentially as follows: the placental circulation is cut off, a progressive diminution of oxygen and a progressive increase in carbon dioxid stimulate the medulla, the baby tries to breathe, fails to get air, and then is slowly killed by gradual poisoning of the medulla.

This explanation is quite adequate if it is assumed that the baby is like a diver with a disabled air pump or a blocked air tube. It assumes that two entirely unproved factors are invariably present, first, that all circulation from the placenta is cut off, and, second, that the baby has an excitable medulla. Both these things may be true, and in that case a progressive asphyxia will eventually kill the baby unless it is delivered. Such a baby, I should suppose, would be deeply cyanotic.

Under the conditions of pressure which must be present during the imposition of serious suprapubic force it seems to me in the highest degree unlikely that the medulla is in the least excitable or is being reached by any appreciable amount of blood, poisoned or otherwise.

I have failed to find any physiologic or clinical evidence to suggest that the pallor and collapse, so often seen, and known as "white asphyxia," have the least connection with the supply of oxygen or carbon dioxid in the blood. Clinically, asphyxiated men never become pale, and experimentally no pallor occurs in asphyxiated animals. On the other hand, there is abundant evidence that exactly the signs seen in babies with "white asphyxia" can be reproduced with ease by disturbances of pressure near the medulla or by obliteration of medullary circulation.

No experimental method for producing anemia of the medulla is, theoretically, more efficient than that used by obstetricians employing traction upon a baby whose head is subjected to continuous severe pressure.

In surgical practice the performance of lumbar puncture upon a patient with high intracranial pressure is regarded as extremely dangerous. Even such slight disturbance of pressure is thought to involve danger of fatal termination of the

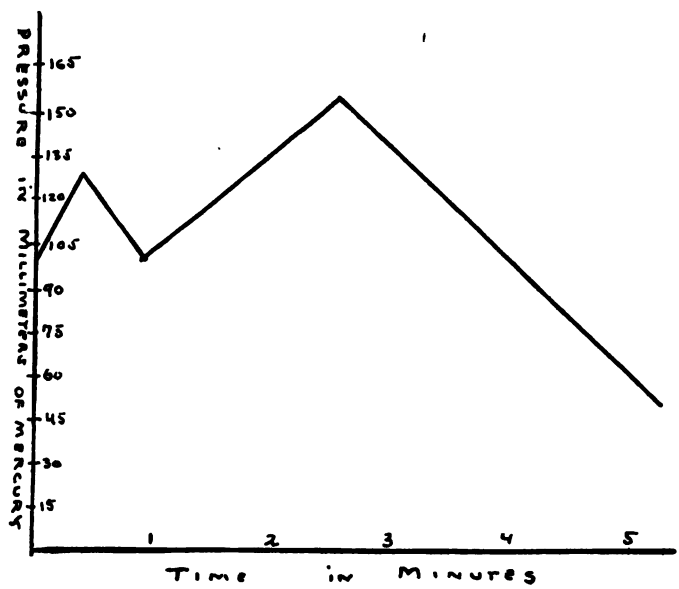

Fig. 250.—Diagram showing blood-pressure following experimental occlusion of blood-supply to brain. After five minutes the blood-pressure remains at 40 mm. for the remainder of the period of occlusion.

medulla. Such an operation is, of course, trivial when compared with the pressure change incident to traction on the fetal spine.

The results of cerebral anemia are well known. Since the time of Astley Cooper physiologists have observed the behavior of animals whose cerebral vessels were tied.

The most interesting and pertinent observations on the effect of occlusion of the cerebral circulation are those of Stewart,

Guthrie, Burns, and Pike. They describe the effect of total occlusion of all cerebral and upper cord circulation as follows: "the nose and the mucosa of the mouth become white as in death, respiration ceases, the reflexes disappear, and the pupils dilate completely. The heart is but little affected." Furthermore, the general blood-pressure first rises and then falls. The time of these changes is shown in a composite chart (Fig. 250).

In a later paper Gomez and Pike showed that the medulla was uninjured histologically after twenty minutes of complete anemia in adult animals. Crile and Dolley showed, experimentally, that puppies can be resuscitated after longer periods of death than adult dogs. Added tenacity of life and earlier exhibition of reflexes after injury to the central nervous system seem characteristic of young animals.

From a consideration of the anatomic and physiologic factors involved I have arrived at a theoretical conception of the course of events in a breech extraction where suprapubic pressure and traction are vigorously used. For what it is worth I present it to you.

The various steps can be suggested diagrammatically.

1. The vertex is pressed on. The supratentorial chamber is put under tension. Enough yielding of the tentorium occurs to force the medulla down; what fluid there is in the ventricles is forced into the spinal chamber and raises pressure there. Almost complete discontinuity of pressure is now established.

2. The blood-pressure changes incident to intracranial tension and, as a result, subtentorial and spinal pressure rises. In the face of continued suprapubic pressure anemia of practically the whole central nervous system occurs. The baby becomes limp and the blood-pressure first rises, and then, after three or four minutes, falls rapidly.

3. On the baby at this stage, collapsed and with a falling blood-pressure, traction is imposed. The high positive intraspinal pressure becomes negative. The force above continues. The medulla almost inevitably becomes impacted.

4. The baby is born limp, with its blood-pressure very low. Mechanically, most of its blood has been forced into its splanch-

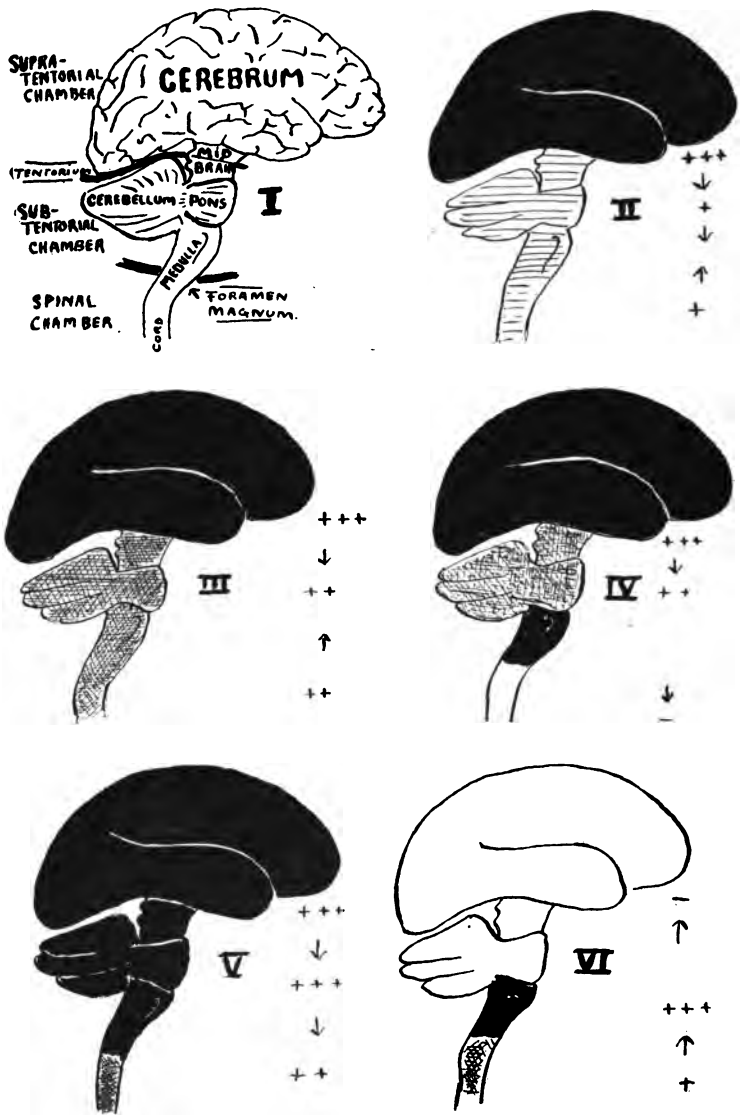

Fig. 251.—I. Normal brain. For diagrammatic clearness the relations are distorted somewhat.

II. Result of pressure in the vertex. A condition of pressure discontinuity is established. The direct pressure affects chiefly the supratentorial portion.

III. Normal pressure relations during pains. The medulla is held be-

nic vessels. The cerebral vessels are empty. The heart is beating.

5. The baby is worked on by the most available, but not necessarily the best trained, person. Frequently the operator himself must revive or repair the mother. Various methods, varying from drenching with hot and cold water to terrifying maneuvers like Schultze's method of resuscitation, are tried in turn. A few white babies survive.

In a physiologic laboratory animals are kept warm and quiet and artificial respiration is handled by beautifully arranged insufflators. The physiologist is able to study his cats for hours without anxiety. The obstetrician rarely saves the collapsed white baby.

The logical treatment of the so-called white asphyxia cases would appear to be along the lines used in shock and hemorrhage.

First, warmth; second, a low position of the head; third, adequate artificial respiration; fourth, efforts to restore the stagnant blood in the splanchnic area to circulation by suitable abdominal binders; fifth, efforts to excite the medulla. To make the medulla excitable is the absolute essential.

There seems no reason to doubt that, if the baby is uninjured and the heart is beating, there is plenty of time to proceed on sound physiologic principles. The medulla gets more of its blood through branches of the vertebrals. If the baby is left alone after delivery carotids will probably get most of the blood that does not stay in the child's abdomen, as the sudden expansion of the head opens very large volume of vessels to be filled. It seems likely that pressure on the carotids would

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tween two equal pressures. Further impaction is prevented by compression of the spinal column, with consequent increase of spinal pressure.

IV. Disturbance of pressure if traction is exerted on the spine during suprapubic pressure. The medulla is forced into canal, when negative pressure is established by serious lengthening of spinal column.

V. Result of tentorial rupture. The whole direct force of the suprapubic pressure is transmitted to the subtentorial chamber.

VI. After delivery the pressure on the vertex is released, throwing open the vessels of the hemispheres and cerebellum. If the medulla is impacted it is a point of great resistance to blood flow, therefore it remains without circulation.

force the blood to flow past the medulla before entering the upper part of the brain. Furthermore, it is not at all certain that the blood contains a proper amount of carbon dioxid. It may well be that it contains too little.

If efforts at restoring medullary activity fail, the chances of benefit from direct efforts to relieve pressure should be considered. Various theoretic possibilities are open; the most logical is direct surgical attack. Various authors note that rupture of the tentorium is possible. This, obviously, would result in subtentorial hemorrhage. In 2 cases I have seen such hemorrhage after breech extraction, though no rupture was looked for. In these cases subtentorial decompression offers a slight chance. The vertebral ruptures are probably hopeless. The impactions might conceivably be relieved.

CONCLUSIONS

The facts about breech extraction appear to be essentially as follows: The general experience all over the world is that the fetal death-rate in breech deliveries is five times that in head cases. If extractions requiring serious operative maneuvers are alone considered, the death-rate must be far greater.

Clinical and pathologic evidence is available to show that gross traumata of the spinal column and the spinal cord are present in a very large proportion of all babies dying during or after extraction.

These traumata are regarded as unfortunate accidents and, if acknowledged, are excused on the ground that the baby inevitably perishes from asphyxia if delivery is not completed very rapidly.

The conclusions to be drawn from these facts are, of course, purely personal. My own belief, based on physiologic considerations, is that asphyxia is grossly overestimated and trauma seriously underestimated by obstetricians. I realize fully, I think, that individual skill and restraint make statistics relatively meaningless.

My explanation of the mechanism of extraction as it affects the central nervous system is somewhat theoretic, of course,

and needs checking up in the delivery room, but it seems probable that disturbances of pressure and of circulation account for the death of many babies.

The following very tentative suggestions are made:

1. Traction, particularly if it involves the whole spinal column, is a totally unphysiologic and highly dangerous procedure. If it is exerted during a period when the brain is under tension, it must result in serious changes of pressure involving the medulla and threatens that organ with impaction in the foramen magnum.

2. Suprapubic pressure is less obviously dangerous, but its persistent application introduces an unphysiologic element. Rupture of the tentorium may follow abrupt or very severe pressure.

3. Efforts to revive the baby should be carried out in a logical way. The careful application of accepted physiologic technic appears to offer the child a better chance than the present methods. Prolonged apnea in animals is frequently followed by complete recovery. As long as the present heroic methods are employed it seems probable that many babies will be sacrificed.

It must be as obvious to my hearers as it is to me that this clinic was worked out in the laboratory and in the library. There are weak links in the chain of evidence. However, it is an attempt to explain on physiologic grounds the disasters that occur in the delivery room.

The important thing is to establish by proper autopsies the facts. This involves not only the observation of blood within the cranium, but the search for its source and the study of the mechanism involved.

A variety of logical lines for further research appear to be open. One of the most obvious is a series of observations on newborn animals to find out the resistance of fetal nervous systems to anemia. Another is the determination of the oxygen and carbon dioxid content of the blood at delivery.

Whether the considerations I have brought before you are valid or not is for those of you who deliver babies to say.

I believe, however, that before version is accepted as a substitute for labor, searching studies of all factors should be made.

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CLINIC OF DR. JOSEPH H. PRATT

FORMERLY OF THE MASSACHUSETTS GENERAL HOSPITAL

ACUTE RHEUMATIC MYOCARDITIS[1]

IN selecting cases for clinical demonstration here in Birmingham at the Hillman Hospital and last week in Atlanta in the medical clinic of Emory University I have been much impressed with the relative rarity of mitral stenosis compared with the number of cases seen in the wards of the Boston hospitals. A large series of interesting cases of heart disease has been available for study, but I have not been able either here or in Atlanta to show a patient who had mitral stenosis with auricular fibrillation. This association is one of the most common pathologic conditions found in heart patients in our northern hospitals.

Mitral stenosis, as you know, is often the end-result of a rheumatic infection on the heart muscle and endocardium occurring years before. If mitral stenosis is rare one would expect rheumatic fever to be infrequent in the South. And it does seem evident from statements made to me by different physicians of large experience that rheumatic fever and chorea are much less common in Georgia and Alabama than in Massachusetts. Dr. E. J. Wood, of Wilmington, North Carolina, who spent a year recently in Great Britain, wrote me that rheumatic fever was much more prevalent in London than in North Carolina. As rheumatic fever injures the heart of almost every child it attacks and leads in a considerable percentage of cases to the development of mitral stenosis, a disease that usually ends the life of its victim before the age of forty, the inhabitants

[1] Clinical lecture to the students of the Graduate School of Medicine, University of Alabama, Hillman Hospital, Birmingham, February 23, 1922.

of a section of the country that is relatively free from this scourge should recognize the advantage they have over those living in less favored places.

The disease is found here, however, and I am going to present a patient who is suffering from rheumatic fever at the present time and whose heart is already severely damaged. I will read an abstract of the clinical record.

Fred S., white male, aged twelve years. He was admitted to the Hillman Hospital February 14, 1922, complaining of pain in the back, shoulders, ankles, and wrists, together with shortness of breath and swelling of the feet.

Family History.—Father well. Mother died of pellagra. One sister is well. There is no history of rheumatic fever or heart disease among his relatives.

Past History.—He was well until 1920, when he had chorea. The onset was sudden and he was helpless for six weeks. It is said that symptoms of chorea returned about Christmas, 1921, but they were slight. His tonsils were removed in 1920. Had pneumonia early in 1921.

Present Illness.—He was seized with rheumatic fever about December 20, 1921, and had chickenpox, it is said, at the same time. The arthritis soon disappeared and he went back to school in January. About February first inflammation of the joints returned. His ankles and wrists were swollen, very painful, and tender. Breathlessness and fatigue on exertion, with an uneasy sensation around the heart were first noticed during the latter part of January. When the patient attempted to walk from his home to his father's store he became so short of breath and so tired that he had to stop on the way to rest, although it was only a short distance and the ground was level.

Dyspnea on effort has continued since that time. He says he cannot climb a flight of stairs without stopping to catch his breath. About February 1st swelling of the legs was first noticed. The edema increased and spread to the body. For six months he has been losing weight. This has been more rapid the past two months, and an increasing pallor has been noted.

On admission there was general anasarca. His temperature

was 100.6° F., pulse 140, respirations 28. When at rest in bed there was no dyspnea.

This boy has marked cardiac insufficiency. That is the first and most important thing for the physician examining him to recognize. The cardiac insufficiency, or heart failure, as some prefer to call it, developed quite suddenly a month ago. Inability to walk a short distance on level ground without breathlessness is evidence of severe cardiac weakness. He had chorea two years ago. We should obtain exact information from the boy or his family regarding his wind before the onset of the present illness. Very likely he could not run without discomfort last fall, as chorea causes myocarditis in a large percentage of cases. If he could not take active exerise at that time without palpitation of the heart or dyspnea, we can be pretty sure that his heart was already damaged before the onset of rheumatic fever last December.

Three weeks ago another sign of a failing heart developed, and that a serious one. It was swelling of the legs. This edema extended over the body, and on admission there was general anasarca. Even now there is slight edema of the chest wall, as is shown by the depression in the skin over the cardiac region made by the bell of my stethoscope. He has, then, two of the chief symptoms of cardiac insufficiency—dyspnea and edema.

I have analyzed the symptoms in 100 cases of cardiac insufficiency seen in my private practice, and the results are given in the table I have placed on the blackboard:

Chief Symptoms in 100 Cases of Cardiac Insufficiency

Dyspnea	74
Pain	40
Edema	33
Cough	29
Tachycardia	24
Pressure	21
Palpitation	14

It would be well to inquire particularly in this case regarding the existence of pain or pressure in the cardiac region, cough, pounding of the heart, and rapid heart action at any time

during his illness. In the clinical history the statement is made that an uneasy sensation around the heart was first noticed the latter part of January. We should get information regarding the nature of this discomfort and its severity. As these symptoms are all so frequently present in the course of heart failure it is a good plan to note those that are absent as well as those that are present. Then any one reading the record knows that an inquiry as to their existence has been made. The majority of my 100 cases were cases of the senile heart. If the 100 cases had been limited to inflammatory disease of the heart muscle and valves, I think the percentage of cases with pain or pressure would have been lower. It is well known, however, that in acute rheumatic myocarditis patients frequently have some pain over the heart and a sense of oppression over the lower sternum is a frequent accompaniment of severe dyspnea. In acute myocarditis with cardiac insufficiency tachycardia is present in a large proportion of the cases, in fact, nearly 100 per cent., while in my series of unselected cases of it will be seen that the percentage is only 24. Palpitation is in my experience much more common in acute mycarditis than in cardiosclerosis.

The symptoms and signs of cardiac failure presented by this lad are certainly due to weakness of the heart muscle, and as this boy presents definite evidence of having rheumatic fever I think you will all agree with me that this weakness of the heart muscle is the result of the action of the rheumatic virus on the heart muscle. Let us first fix our attention on the heart muscle and disregard the condition of the valves. Acute myocarditis may occur, as you know, as a complication or sequela of typhoid fever and diphtheria and other infectious diseases, but it most frequently develops in the course of rheumatic fever. Myocarditis rheumatica develops in from one-third to one-half of all cases of rheumatic fever.

It can be distinguished from other forms of acute myocarditis by the pathologist on microscopic examination, although to the naked eye nothing characteristic of rheumatic infection is seen. The lesion that enables one to recognize a rheumatic heart is a collection of peculiar cells forming a nodule smaller than a miliary

tubercle. This nodule is composed of large cells that develop from the connective tissue, intermixed with lymphocytes, plasma cells, and eosinophilic leukocytes. These large cells contain one or more vesicular nuclei. The protoplasm is granular and takes a deep red color with methyl-green pyronin. This lesion was first described by Aschoff and bears his name. These submiliary nodules are most numerous in the subendocardial tissue. Numerous branches of the conducting system of the heart are situated here, and these are often destroyed by the development of Aschoff's bodies. They are probably found only in cases of acute rheumatic fever and in acute chorea, although some investigators maintain they are non-specific and are present in other conditions than rheumatic infections. The subject deserves further study. Streptococci injected into animals do not produce these characteristic nodules (Fränkel). It is claimed, however, that the sterile blood of rheumatic patients when injected into animals sets up myocardial changes in the form of these perivascular bodies (de Vecchi).

Delay in the conduction of the impulse from auricle to ventricle in the course of rheumatic fever is the most trustworthy sign of the existence of acute myocarditis. It was present in 30 per cent. of the cases of rheumatic fever in which routine examinations were made by means of the polygraph and electrocardiograph (Parkinson, Gosse, and Gunsen). I remember well a case with fever of unknown nature admitted to the Massachusetts General Hospital in which a graphic record enabled us to make a diagnosis of acute myocarditis. The heart appeared normal on physical examination. There was no arthritis. The patient, a young woman, serving as cook in a physician's family, was evidently quite sick, but there were no localizing symptoms. No suspicion of rheumatic myocarditis was entertained until I made a tracing of the jugular pulse, which showed a marked increase in the conduction time from the auricle to the ventricle. This finding alone showed we were dealing in all probability with a rheumatic infection that had involved the heart. You sometimes hear the statement made that polygraph tracings teach nothing about a case that cannot be learned in the ordinary

physical examination. This is not true. The information furnished by a jugular tracing or an electrocardiogram in cases of suspected rheumatic myocarditis is most important, as I have just shown, and it cannot be obtained without these instrumental aids. I know from personal experience that the making and interpreting of graphic records in the study of the heart cases in private practice adds greatly to the interest and scientific value of one's routine work. I hope a tracing of the jugular pulse will be made in this case.

The chief evidence in favor of acute myocarditis in this lad is the history of progressive cardiac insufficiency beginning only a month ago. He still has mild rheumatic arthritis involving chiefly the wrists and ankles. This may account for the slight fever he has had since admission. The maximum temperature has been 100.2° F.[1] It has not been above 99° F. the past four days. The pulse range has been from 90 to 110. This is without special significance. Although tachycardia is a wellnigh constant symptom in acute rheumatic myocarditis this slight acceleration might occur in rheumatic fever without cardiac involvement.

On examing the cardiac area I cannot see or feel the cardiac impulse, but on precussion enlargement of the cardiac area is easily made out. The area of absolute cardiac dulness is that portion of the heart's surface not covered by the lungs, which normally extends from the left sternal margin to about the left parasternal line, reaches in this patient from the right sternal margin to a line about 1 cm. outside the nipple line. The relative cardiac dulness begins at the right sternal margin and its left border is some distance beyond the nipple line. The heart then appears to be enlarged to the left. This finding is confirmed by the radiogram taken at a distance of 2 meters from the tube. This gives a silhouette of the actual size of the heart. You can see there is general enlargement of all diameters.

On auscultation of the heart it is well to note first the char-

[1] Five days after I demonstrated this case pain and swelling developed in the left elbow and the temperature rose to 101.8° F., and the following day to 103° F. The inflammation then shifted to the right elbow.

acter of the sounds, and only after this has been determined to fix the attention on any murmurs that may be present. The first sound at the apex is loud and somewhat snapping. The second sound is barely audible at the apex, but is well heard at the base, although not pathologically accentuated over the pulmonary area. A loud systolic murmur accompanies the first sound at the mitral and tricuspid areas.

Twenty years ago the significance of this murmur would not have been questioned by most clinical teachers. It would have been regarded as positive evidence of endocarditis of the mitral valve and the case diagnosed as rheumatic fever with mitral insufficiency of valvular origin. But even twenty years ago a few wise ones knew that in rheumatic fever even a loud systolic murmur might occur at the apex in the absence of valvular disease. This murmur may be due to one of three causes: (1) Inflammation of the mitral valve with regurgitation. (2) The action of the unknown toxin of rheumatic fever on the muscular ring surrounding the mitral valve without anatomic changes in the muscle, a so-called functional murmur. (3) Actual inflammation of the portion of the heart muscle to which the valve segments are attached. This would include the papillary muscles as well as the muscular ring.

It is probable that all three causes contribute to the production of the murmur in this case. It would be illuminating to know the condition presented by this boy's heart before the present illness. It is probable, in view of the history of chorea two years ago, that enlargement of the heart was even then present, as well as a mitral systolic murmur. If so, the boy had at that time a chronic endomyocarditis. I wish to make clear the point that an apical systolic murmur appearing in the course of rheumatic fever may be due to changes in the heart muscle and not to disease of the valves. In fact, acute endocarditis may develop without the formation of a murmur or the appearance of symptoms. This frequently occurs in pneumonia, as autopsy findings prove.

The liver of the patient is not enlarged. The abdomen is natural. There is slight subcutaneous edema persisting.

In studying cases of rheumatic fever in children we should always examine the blood and determine the degree of anemia. It is said that there is no infectious disease except diphtheria in which a rapidly developing anemia so regularly occurs as in rheumatic fever. This boy's pallor was first noted two months ago. Unfortunately, I have not got the laboratory reports on the case, but I think he has a moderate anemia. It is well to determine the percentage of hemoglobin and to count the erythrocytes frequently during the course of rheumatic fever. A careful search should also be made now and at intervals throughout his stay in the hospital for the presence of subcutaneous fibrous nodules, the significance of which I will show later.

We are dealing in this case, as has been shown, with two conditions of great importance: (1) Severe cardiac insufficiency, the result of acute rheumatic myocarditis, and (2) the rheumatic infection itself, as it manifests itself in children.

The rheumatic virus rarely if ever attacks the endocardium alone, and hence the common term "acute rheumatic endocarditis" is incorrect and misleading. Usually, as pathologic studies show, the endocardium, myocardium, and pericardium are all attacked in different degree. In many cases microscopic lesions are found in one or more of these structures that present a normal appearance to the naked eye. The old word "carditis," introduced by Corvisart over a century ago, has been revived and applied to the rheumatic heart. "Pancarditis" is the term sometimes used, and this is even more accurate than carditis. When symptoms of embarrassed heart action occur in rheumatic infection it is practically always due to a severely damaged myocardium, and the symptoms described in textbooks as occurring in acute rheumatic endocarditis are really due to the accompanying myocarditis.

Two symptoms I have found especially helpful in the recognition of acute myocarditis in the course of a rheumatic infection: (1) Change in the heart rhythm, usually a regular tachycardia, but sometimes an irregular pulse, due to heart-block, and in one instance a bradycardia possibly the result of complete heart-block; (2) dilatation of the heart.

The tachycardia may persist for weeks or months and is increased by slight physical exertion or emotion. With a temperature not above 99.5° F. it is frequent to find the pulse-rate ranging from 110 to 120. In 11 cases of acute rheumatic myocarditis seen in a series of 230 cases of heart disease in my private consultation practice the pulse was rapid in 9, slow in 2. In those with accelerated pulse the rate at the time of my examination ranged from 90 to 140. One of the cases with a slow pulse was in a patient with mitral stenosis and auricular fibrillation of many years' duration, in which the pulse was kept slow by digitalis during a severe attack of acute myocarditis and pericarditis. The other was a suddenly developing bradycardia, rate 45 to 52, following rheumatic arthritis. The heart was greatly dilated, but as I could not obtain a tracing of the jugular pulse the nature of the bradycardia was not determined.

The patient with the lowest rate (90) in the group with rapid heart action had previous to the time I saw him a pulse-rate ranging from 100 to 130 for several weeks. He was a boy aged sixteen, who on January 14, 1917 was seized with vomiting and diarrhea. Fever, malaise, and abdominal pain followed. A few days later the feet became painful and tender, but were not red or swollen. Later the wrists and elbows were involved and the pain was severe. The fever was not high, maximum temperature being 103° F. As the temperature began to fall about January 25th the pulse-rate began to rise, reaching a maximum of 130. After March 17th the temperature rarely rose above 99° F. When I first saw him with his physician, Dr. W. D. Walker, of Andover, Mass., in May, 1917 the heart was greatly dilated and aortic and mitral insufficiency were present. The slow and gradual fall in the pulse-rate after this date, as his condition improved, is shown in the table on page 1314.

TABLE I

Edward C. Acute Rheumatic Myocarditis. Pulse-rates from March 17th to August 19th.

	Pulse-rates.	Average rate.
March 17th–April 6th	88–116	100
April 7th–27th	88–112	95
April 28th–May 18th	78–108	90
May 19th–June 8th	76–94	80
June 9th–29th	75–94	82
June 30th–July 20th	72–82	78
July 21st–August 10th	68–90	78
August 11th–19th	68–82	75

When I saw him on September 12, 1917 the pulse was 64. This patient did not leave his bed from the onset in January until the middle of May, when he was allowed to walk to the bathroom. In August he was allowed to walk down stairs, but was carried upstairs. In September he was still having his meals in bed, but was allowed to sit up three to four hours a day.

Dilatation of the heart occurs more frequently in rheumatic disease than in any other infection. It can usually be recognized by inspection and palpation as well as by percussion. It may develop to a serious extent within a week or two after the first appearance of any symptoms of illness. Only yesterday I saw with Dr. Snyder and Dr. Lester a little girl with rheumatic myocarditis in which distinct dilatation was detected by Dr. Lester at his first visit, and the child had then been ill only two days. I have previously seen marked dilatation of the heart present a few days after a murmur was first heard.

In one case the heart sounds were clear in both the erect and recumbent position, but the cardiac impulse in the fifth interspace extended from the nipple to the anterior axillary line and was increased in force. Percussion and a teleradiogram showed marked enlargement of the heart.

In 7 of my 11 cases there was a *wide area of visible and palpable cardiac impulse.* In 5 of my cases in which the record is precise the impulse was plainly seen in three interspaces, reaching as high as the second interspace in 3 and the third interspace in all 5. Lees, an English physician, also emphasized years ago

the frequency of a wide area of cardiac impulse in the acute rheumatic heart. The increase in the percussion area in my experience has been chiefly to the left. In no case in my small series was there definite dulness to the right of the median line. After the subsidence of the inflammation there may be a striking reduction in the size of the heart as determined in teleradiograms. This was well shown in the case of Donald A., aged seven.

TABLE II

Measurements of the Heart of Donald A. in Teleradiograms: (A) During Acute Rheumatic Myocarditis; (B) After Recovery

		A. October 30, 1920.	B. April 19, 1921.
Distance of right border from median line	Mr.	3.5	3.3
Distance of left border from median line	Ml.	9.0	7.0
Transverse diameter	Tr.	12.5	10.3
Length of heart	L.	12.5	11.4
Diameter of the base	Br.	8.2	7.5
Diameter of great vessels		4.5	4.0

I have been repeatedly struck with the fact that physicians with whom I have seen cases paid a great deal of attention to the presence of murmurs, the significance of which was often doubtful, and very little attention to inspection and palpation and percussion, which, as I have pointed out, yielded results of great importance and which offered no difficulty in interpretation.

Now let us turn our attention to the rheumatic infection itself as it occurs in children. While in adults severe arthritis is most prominent in the clinical picture presented by rheumatic fever and the heart frequently escapes injury, in children the arthritis is usually slight and fleeting and the heart bears the brunt of the attack. Physicians are often misled into thinking the condition is trivial because the joint symptoms are so mild. In the case under discussion the joint pains which developed in December quickly disappeared and the boy was sent back to school. The inflammation of the heart muscle probably began about the same time as the arthritis in December, and was progressive without producing noticeable symptoms or signs.

So great was the damage that by the end of January that the dyspnea due to heart weakness appeared on slight exertion.

Sometimes there is no arthritis to warn the observer of the onset of this serious disease. In fact, the rheumatic infection may involve the heart before there is evidence of local disease elsewhere. Dr. Paul White reported a case in which heart-block developed before the onset of acute rheumatic arthritis. We are still accustomed to regard arthritis as the essential feature in rheumatic fever and any associated affections of other parts as mere complications, although Cheadle showed many years ago in his Harveian Lectures "that articular inflammation is only one of many direct and sometimes independent manifestations of the rheumatic state."

Arthritis is, then, only one member of the rheumatic series. There are quite a number of links in the rheumatic chain, any of which may be absent. In adults in addition to carditis and arthritis are tonsillitis, pleurisy, and myositis. In children other manifestations appear that are rarely met with in later life. They are chorea, subcutaneous fibroid nodules, and exudative erythema. Purpura is often classed as a rheumatic manifestation, as the term "purpura rheumatica" indicates. Purpura, although it does rarely occur in rheumatism as in all infectious diseases, in my opinion does not properly belong in the rheumatic series. Purpura was associated with rheumatism in only 4 out of 64 cases of secondary purpura I collected from the records of the Johns Hopkins and Massachusetts General Hospital.

Rheumatic tonsillitis is frequent both in children and adults. It resembles ordinary acute tonsillitis except that it is preceded or followed by some other rheumatic manifestation, often myocarditis and endocarditis. If the rheumatic infective agent attacks the nervous system, chorea results. In no other infectious disease is endocarditis so frequently found at autopsy as in chorea (Osler).

St. Lawrence recently read a paper in Boston in which he stated that of 49 patients with chorea whose hearts were normal when they first came under his supervision, 16, or 30 per cent., contracted a lesion in the heart during the period of observation

which extended over several years. The heart is usually involved late in the course of an attack of chorea.

The importance of subcutaneous fibroid nodules in the diagnosis of rheumatic infection is not generally realized and a search for them rarely made. In structure they are similar to Aschoff's nodules in the heart, and, like the latter, they probably occur only in cases of rheumatic infection. They are rare in adults, but common in rheumatic children, especially in those with severe inflammation of the heart. Cheadle, in London, saw only 2 cases in adults, but "scores in children." Most American writers on diseases of children state that although common in England they are rare in this country. Brennemann, of Chicago, who in recent years has been especially interested in these nodules and has really looked for them, states that he is convinced that they occur quite as frequently in the severer type of rheumatic disease in America as in England. Swift, in a recent monograph on rheumatic fever, says he has found them commonly in New York. They vary in size from 1 mm. to 2 cm. and are sometimes to be felt rather than seen. They vary in number from 1 to 100 or more; usually 8 or 10 are found. They are often located upon the back of the elbow, over the malleoli and near the patella. The neighborhood of the joints and the skin over the muscles should be carefully palpated. They are not connected with the skin and are usually painless. They occur most commonly after the acute symptoms of the rheumatic fever have subsided.

Erythema nodosum was present in one of my cases associated with rheumatic pleurisy, pericarditis, and myositis. I have only once had a case of acute myocarditis in which erythema exsudativium multiforme occurred as a rheumatic manifestation.

The patient we have seen today will probably recover from this attack of rheumatic infection, as the immediate mortality is low. The first sound of the heart at the mitral area is already suggestive of the sharp snapping sound so characteristic of mitral stenosis, and it is not unlikely that in a year from now definite signs of mitral stenosis with insufficiency will be present.

Mitral stenosis is due in practically all cases, I believe, to a

rheumatic infection. I have never seen a case in which any other cause could be definitely assigned, and I have found none in the literature. Yet I could obtain a definite history of rheumatic fever in only 6 out of 21 cases of mitral stenosis I have seen in private practice and analyzed for this purpose. "Growing pains" had been present in 2 other cases and chorea in one. The conclusion seems obvious that if mitral stenosis is due to rheumatic infection the manifestations were so slight that they were ignored or had been forgotten. If, as some French observers claim, 50 per cent. of the cases of pure mitral stenosis are due to other causes than rheumatism, such as scarlet fever, tuberculosis, whooping-cough, typhoid fever, strain, etc., one would expect to find about 50 per cent. as many cases in the southern clinics as in the northern, but there seems to be much less than that proportion here. Furthermore, the percentage of cases of mitral stenosis in the South giving a history of rheumatic fever seems to be about the same as in regions where rheumatic fever is more prevalent.

CLINIC OF DR. WILLIAM D. REID

BOSTON CITY HOSPITAL

CARDIOVASCULAR SYPHILIS

INFECTION of the heart and aorta by the spirochete of syphilis produces one of the most important types of heart disease. Statistics[1] from various clinics indicate the presence of cardiovascular syphilis in 3.5 to 7 per cent. of the total autopsies and 75 to 85 per cent. of the autopsies on bodies known to have been infected with syphilis.

Etiology.—Certain lesions of the heart and aorta have long been associated with syphilis, but it has been only since the demonstration of the spirochete in the aortic wall in 1906 and 1907 by Reuta,[2] Benda,[3] and Schmorl,[4] and in the myocardium by Warthin[5] in 1916 that the true nature of cardiovascular syphilis has been understood. It is now generally conceded that the lesions are due to the actual invasion of the circulatory tissues by the pale spirochete.

The involvement of the heart may begin before or during the secondary stage, so-called, of syphilis. However, sixteen years was the average period elapsing between the chancre and the appearance of symptoms of circulatory disease in the cases treated at the Massachusetts General Hospital[6]; the shortest was six months and the longest thirty-three years.

Men are attacked about three times as frequently as women. The age period from thirty-five to fifty years supplies the great-

[1] Reid, W. D.: Boston Med. and Surg. Jour., clxxxiii, 3, 67 and 4, 105, July 15 and 22, 1920.

[2] Reuta: Munch. med. Woch., liii, 778, 1906.

[3] Benda, C.: Berlin. klin. Woch., xliii, 989, 1906.

[4] Schmorl: Münch. med. Woch., liv, 188, 1907.

[5] Warthin, A. S.: Amer. Jour. Med. Sci., cliii, 508, 1916.

[6] Reid, W. D.: Jour. Amer. Med. Assoc., lxxiii, 1832, 1919.

est number of cases. According to Allbutt,[1] congenital cases are not infrequent at the years fifteen to twenty and they are common in syphilitic infants. Laborious or athletic pursuits appear to be important determinants. Alcohol is probably unimportant, as the disease occurs in total abstainers.

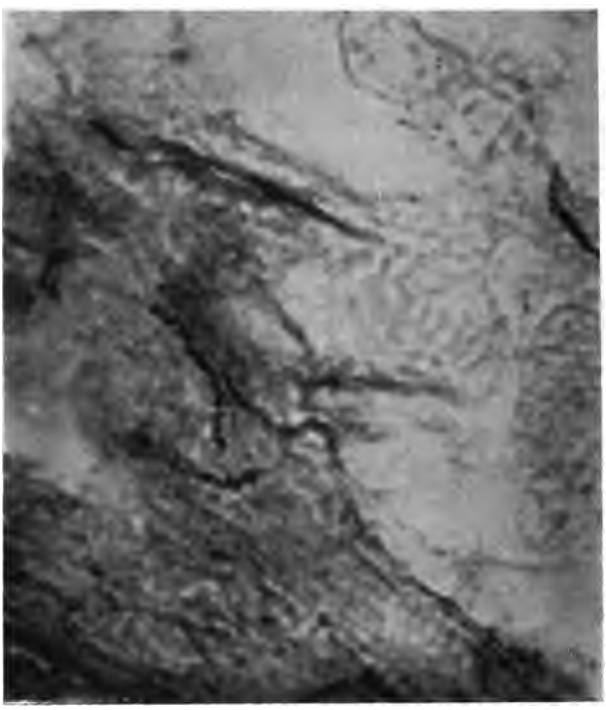


Fig. 252.—Spirochæta pallida in myocardium. (Courtesy of A. S. Warthin.)

Pathology.—In recent years there has been an appreciation of the fact that coincident with the syphilitic lesion in the aorta the heart proper is usually involved. To the naked eye the heart may show dilatation, hypertrophy, atrophy, and patches of fibrosis in the wall of the left ventricle. In congenital cases the wall of the right ventricle may be chiefly affected.[2]

[1] Allbutt, C.: "Diseases of the Arteries, including Angina Pectoris," 1915, Macmillan & Co., 2, 140.

[2] Warthin, A. S.: Amer. Jour. Syphilis, 2, 425, July, 1915.

In many cases the fibrous changes are detected only by microscopic examination. To follow Warthin's description,[1] the essential lesion is an interstitial myocarditis characterized by infiltration with lymphocytes and plasma-cells along the vessels between the muscle-fibers. The entire heart wall from epicardium to endocardium, including the papillary muscles, may be involved in the infiltrations; but in the average case they lie nearer to the endocardium. In the great majority there are areas of healing by fibrosis associated with areas in which the process is active. A progressive fibrosis of the heart muscle eventually takes place in all cases.

Sclerosis of the larger branches of the coronary arteries is rare, even in cases affected by angina pectoris. In the most severe cases there is infiltration around the smaller arteries. An aneurysm of the wall of the left ventricle near the apex is not uncommon. True gummata in the myocardium are relatively rare.

The aortic valves showed slight to moderate fibrous thickening in about two-thirds of the Massachusetts General Hospital cases, while in another 10 per cent. the damage was more extensive. The correlation of the clinical and postmortem evidence indicated that the insufficiency of the aortic valve, found clinically in 40 per cent. of the cases, is more often dependent upon a yielding of the aortic ring than upon actual damage to the valve curtains. Aortic stenosis is a great rarity. Syphilitic changes of the auriculoventricular valves apparently do not occur.[2, 3]

There is much variation in the extent of the pathologic changes in the arterial system. The lesions are mostly found in the wall of the aorta, and predominatingly in the ascending and transverse arch. This aspect of cardiovascular syphilis has been so evident that the disease is commonly referred to in the literature as syphilitic aortitis. In 94 per cent. of the group of autopsies referred to above the ascending portion

[1] Warthin, A. S.: Amer. Jour. Syphilis, 2, 425, July, 1915.
[2] Ibid.
[3] Brooks, H.: Amer. Jour. Syphilis, 52, 217, April, 1921.

of the arch was affected, but not infrequently the process was as extensive in the transverse arch, and sometimes more so.

The primary seat of the aortitis is along the vasa vasorum in the adventitia; the media is soon involved and the intima last of all. Around these vasa vasorum are found collections of plasma and lymphoid cells, and, in the more acute foci, the treponemata may be demonstrated by the Levaditi silver impregnation method. A definite gumma is rare. There may be large areas of healing by scar. It is the irregular distribution of the fibrosis and the necrosis, *i. e.*, the reparative and the destructive changes, which gives the irregular puckered appearance to the aortic wall in cases of advanced aortitis. The absence of calcification in the luetic lesion is a contrast with its prevalence in arteriosclerosis. Warthin[1] emphasizes that the pathologic diagnosis of syphilis is essentially microscopic, as to the unaided eye the tissue may appear sound.

When the process has caused the aorta to dilate considerably it is often a matter of personal choice with the examiner whether he employs the term "syphilitic aortitis with dilatation" or "syphilitic aortitis with aneurysm." There is no hard-and-fast line between the two conditions. Large aneurysms of the saccular or dissecting types may occur. These big aneurysms involve adjacent structures by pressure, and by a process of erosion may penetrate and finally rupture with fatal hemorrhage into the pericardial sac, the chest wall, trachea, esophagus, etc. A great majority of aneurysms which involve the aorta before it pierces the diaphragm are due to syphilis, but rarely,[2] usually of the small saccular type, they may result from nonluetic infections.

Symptoms.—Cardiovascular syphilis is, for the most part, insidious. Such symptoms as occur are mainly due to the cardiac lesions rather than to those of the aorta, save for the symptoms caused by pressure when an aneurysm has been formed. It does not seem practical to classify the cases in relation to the anatomic lesion, but perhaps they may better be

[1] Warthin, A. S.: Amer. Jour. Syphilis, 2, 425, July, 1915.
[2] Reid, loc. cit.

divided into acute or chronic according to the intensity of the symptoms. Tides of activity may occur.

If there be symptoms, pain is prominent. It varies from a sense of tightness or burning about the upper sternum to the utter torture of severe angina. It may come in attacks, be associated with exertion, or be present almost continuously. In location and radiation the pain of cardiovascular syphilis is wont to resemble that of angina pectoris.

Shortness of breath is common. It may be associated with rapid heart action and other evidence of cardiac embarrassment. Cough and weakness are further symptoms.

Fever of a low-grade "septic" or irregular type may occur, but is of little diagnostic value, as it is rare that careful examination of the patient fails to show the presence of some other condition which might cause the rise in temperature. Also, of course, fever may be present at various times in syphilis, but it does not *per se* indicate invasion of the circulatory tissues.

In cases in which the luetic infection has seriously impaired the integrity of the heart and aorta, symptoms consistent with advanced heart failure will be in evidence.

When an aneurysm is present as a complication, pressure symptoms may arise. A rather strident whistling respiration on exertion, while by no means an initial sign, may yet long precede other respiratory signs as a symptom of pressure. A "brassy cough" and partial aphonia are frequent results of involvement of the left recurrent laryngeal nerve in its course around the arch of the aorta. The direction in which pressure is exerted by an aneurysm and the rapidity with which dilatation occurs and grows are undoubtedly determining factors in the production or absence of symptoms.

Physical Signs.—The evidence of luetic infection of the heart and aorta obtained by physical examination varies according to the nature and extent of the lesions present. In many cases physical signs may be essentially absent. They may be considered to best advantage, perhaps, under inspection, palpation, percussion, and auscultation.

Inspection is of value only in advanced cases. Thus, a

visible throbbing of the carotids suggests insufficiency of the aortic valve, which in most cases in adults is known to be syphilitic in origin. A visible pulsation in the suprasternal notch may indicate a dilated aortic arch. Again, any visible pulsation in the second or third intercostal space suggests aneurysm. Great enlargement of cervical veins may be noted, but should not be expected save with cases complicated by aneurysm and with other signs of pressure. Inequality of the pupils from irritation of the cervical sympathetic may occur.

Palpation.—A palpable impulse in the suprasternal notch, due to dilatation of the arch of the aorta, is, at best, not a particularly reliable sign, as it is not always present and also occurs in arteriosclerosis and in some conditions which are not truly disease. In case aortic regurgitation is present the apex impulse is usually moved downward and to the left and is accompanied by the Corrigan or collapsing type of pulse. An expansile pulsation lateral to the upper end of the sternum is strong, but not absolute, evidence of aneurysm.

Percussion may be useful to detect enlargement of the first part of the aorta. The supracardiac dulness is most marked in the midmanubrial region and commonly the dulness is greater to the right than to the left. In rare instances an area of dulness has been detected to the left of the third and fourth dorsal vertebræ, due to a dilatation or aneurysm of the adjacent aorta.

Auscultation.—The second sound at the second right costal cartilage often is of a duller note than normal, but practically the same quality may occur in arteriosclerosis. A systolic murmur, often very faint and soft, but sometimes loud and rough, at the aortic area is frequently present in cardiovascular syphilis. Occasionally it is accompanied by a thrill, not necessarily indicating a stenotic change in the aortic orifice. If the luetic infection has caused an insufficiency of the aortic valve the characteristic diastolic murmur of aortic regurgitation will be noted. This, of course, may or may not mask the second sound. At the apex a systolic murmur, due to an insufficiency of the mitral valve and of muscular origin, is commonly present in addition to the aortic findings. And in some cases the Austin

Flint murmur at the apex may be a further finding. A friction-rub at the base has been reported.

An abnormal rhythm may control the heart. Partial or complete heart-block, resulting from myocardial lesions, is particularly prone to occur. Premature beats are common. Less frequently auricular fibrillation or other arhythmia may obtain.

There is nothing characteristic in the *blood-pressure* readings in cardiovascular syphilis; it remains essentially normal unless aortic regurgitation or some condition (not syphilitic) causing hypertension complicates the case.

As in other forms of syphilis, the *Wassermann reaction* has been found to vary from strongly positive to negative. There were 7, or 25 per cent., full negative results in twenty-seven Wassermann tests performed in the above quoted[1] group of cases proved shortly afterward at autopsy to have definite cardiovascular syphilis.

Roentgen Findings.—It is inconsistent with our knowledge of the pathology of cardiovascular syphilis to expect that evidence of its presence can be obtained in early cases by radiographic examination. But in the more advanced cases, particularly when the aorta has undergone alteration in size or contour, the *x*-ray often produces very definite findings.

A marked prominence of the aortic shadow to the right, just above that of the right auricle, is almost always due to syphilitic aortitis. A general enlargement of the shadow of the aorta may occur, but must be distinguished from the changes in the aortic curve occurring in some other conditions. An aneurysm, if present, is usually demonstrated on radiographic examination. The value of this is better appreciated when it is remembered that in one-half of the cases of the saccular type there are no sounds or murmurs over the aneurysm.

If the width of the great vessels, obtained by Roentgen mensuration, is more than that of the heart, syphilitic invasion of the aorta is almost certainly present. In doubtful cases the mensuration should be repeated in a few weeks or months to

[1] Reid, loc. cit.

note if the aorta is increasing in size. The heart often shows enlargement more markedly in its long diameter, and especially in those cases in which insufficiency of the aortic valve is a feature.

Diagnosis.—A clear distinction must be made between "syphilis of the heart" and "the heart in syphilis," as it seems established that the heart is not involved in every patient suffering from syphilis. On the other hand, it is the part of wisdom to consider every patient known to have syphilis as a potential case of cardiovascular syphilis.

Syphilis should be considered in any case of cardiovascular degeneration of obscure origin. Every case of aortic insufficiency or heart-block developing in an adult not giving a clear history of rheumatic infection should at once rouse the suspicion of specific disease. A definite history of syphilitic infection and a positive Wassermann reaction are of considerable value, but they may be absent. The observation of syphilitic skin lesions, or some other mark of lues, may suffice to turn a possible into a probable diagnosis of cardiovascular syphilis. The *x*-ray, in all but very early cases, usually gives the most definite confirmatory findings.

Though easy to diagnose in a typical or advanced case, cardiovascular syphilis is almost impossible to diagnose in the early or latent type. There is no one point on which a diagnosis is to be made, but each suspected case requires careful attention to the history, especially to the symptoms and physical findings, and is to be checked up by radiographic examination and Wassermann test. It is only after all the facts have been collected that definite conclusions should be drawn, and at times only a tentative diagnosis is possible. And in this position the diagnosis may remain until the result of the therapeutic test for syphilis has been observed. This consists preferably of four to six injections of arsphenamin at weekly intervals followed by a course of seven to eight intramuscular injections of a mercurial salt. Of less value, but for certain reasons sometimes employed, is the oral administration of hydrargyrum cum creta, 0.06 to 0.12 gm. (1 to 2 gr.) t. i. d., with 0.3 to 1.2 gm. (5 to 20 gr.) of potassium iodid t. i. d. for about six weeks.

Differential Diagnosis.—*Non-syphilitic aortitis* occurs[1] in rheumatic fever, influenza, septic heart disease, anthrax, erysipelas, smallpox, typhoid fever, diphtheria, measles, scarlet fever, pneumonia, malaria, tuberculosis, and gonorrhea. It is relatively rare, often symptomless, and usually overlooked. Even small aneurysms or perforation may occur. Bennert[2] has established a rule that aneurysm in children and in youths is a result of acute rheumatic fever. They are rare and happily have a marked tendency toward spontaneous recovery. It is perhaps enough to realize the existence of these non-syphilitic infections of the aorta, and in a case of aortitis occurring after one of the above-mentioned infections the possibility of its non-syphilitic origin should be considered.

Arteriosclerosis is often combined with syphilis in elderly patients. Pure atheroma rarely causes insufficiency of the aortic valve and practically never leads to the formation of an aneurysm. Pain is present in but a small minority of the arteriosclerotic cases. The gross pathologic findings differ, particularly in that there are fatty and calcareous changes as contrasted to the fibrosis of syphilis. The Roentgen findings of the aorta show no bulging of the ascending aorta to the right, and less dilatation of the arch, but rather a lengthening of the same with a prominence of the knob to the left.

Hypertensive heart disease also causes enlargement of the heart and some dilatation of the aorta, but may be dismissed with the comment that neither high blood-pressure nor evidence of impaired renal function forms part of the picture of cardiovascular syphilis.

Rheumatic heart disease at times must be considered. This is especially true if, in addition to the findings of aortic insufficiency, there is an apical murmur which may be explained either as that described by Austin Flint or as that of true stenosis of the mitral orifice. Organic change of the mitral valve is probably never syphilitic, and if present the insufficiency of the aortic valve may then also be of rheumatic origin. Evidence

[1] Reid, loc. cit.

[2] Bennert, R.: Zeitsch. f. klin. Med., Bd. lxix, Nos. 1 and 2, 121.

of enlargement of the left auricle and the electrocardiographic findings of mitral stenosis (high P wave and right ventricular preponderance) indicate the latter condition. True mitral stenosis, furthermore, tends to distinctly lessen the Corrigan quality of the pulse. The history is often of assistance; "apparently well until recently" and the absence of the story of an infection which might cause rheumatic heart disease is not the history of a rheumatic heart. Nevertheless, there are cases in which a distinct doubt must remain. Resort to the therapeutic test of antisyphilitic treatment is then justifiable.

Heart-block may likewise raise the question as to whether it be of rheumatic or luetic causation. The therapeutic test is indicated in these cases also.

Cases in a sanatorium for *pulmonary tuberculosis* have not infrequently first been correctly diagnosed cardiovascular syphilis as a result of radiographic examination.

Mediastinal tumors may at times offer some difficulty in differentiation. A careful study with a consideration of the data present, and especially the *x*-ray findings, will almost always enable the correct diagnosis to be made.

Tabes dorsalis hardly needs differentiation, save as regards the so-called cardiac crises in tabetic patients. As syphilitic infection of the heart and aorta is very common in the victims of tabes dorsalis, the practical importance of separating the cardiac crises in tabes from the anginal attacks of cardiovascular syphilis, if they be not one and the same condition, is much lessened.

Prognosis.—On the whole, the prognosis of syphilitic infection of the circulatory tissues is grave because of the tendency to progressive impairment of the integrity of the heart and aorta. Angina pectoris with its danger of sudden death may ensue. About 30 per cent. of the recognized cases (figures are of little value, as cardiovascular syphilis often escapes recognition) are estimated to develop aneurysm or insufficiency of the aortic valve, or both. A fatal hemorrhage from perforation of the aneurysm is not unusual.

On the other hand, evidence is now being accumulated that

modern antisyphilitic therapy is being attended with promising results. The improvement is in symptoms and not in physical signs. Thus, diminution of the dilatation of the arch of the aorta does not occur. Recollection of the pathology of cardiovascular syphilis makes it easy to comprehend why aneurysm, aortic insufficiency, etc., cannot be removed. The average length of life in cases of a comparatively advanced type at the time treatment was instituted[1] was one year, when mercury and potassium iodid were employed, and three years, when diarsenol, or its equivalent, was added.

Considerable depends upon the amount of damage already incurred before the diagnosis is established and treatment instituted. Thus, if insufficiency of the aortic valve has ensued, serious mischief has been achieved. Cardiac failure, especially if advanced to the stage of edema of the lower extremities, always offers a poor prognosis.

Treatment.—This is primarily that of syphilis. Since it has been demonstrated that the spirochetes actually invade the heart and the aorta, the treatment should be directed toward destroying the invading organism as quickly as possible. For this purpose arsphenamin, or its equivalent, and mercury are most useful. Syphilographers, however, differ in the details of the administration of these drugs. The relative merits of the methods advised by different authorities need not be entered into for the purpose of this paper. A single method[2] will be described which is suitable for the treatment of cardiovascular syphilis and, in addition, appears to be attended with a minimum of risk and has been observed to obtain favorable results.

Arsphenamin, or a similar arsenical, should be injected intravenously in an initial dosage of about 0.15 gm., and, if well tolerated, rapidly increased to 0.5 gm. per dose. This latter amount should rarely be exceeded, as with this precaution cardiac cases may be treated with but small risk of the occurrence of an unpleasant reaction. The course of arsphenamin

[1] Reid, W. D.: Jour. Amer. Med. Assoc., lxxiii, 1832, 1919.

[2] The writer is not a syphilographer; he is indebted in part to Austin Cheever, of Boston, for the details of the antisyphilitic therapy.

should include six to ten injections at weekly intervals. At the same time the patient should receive mercury by mouth; suitable preparations are the protiodid of mercury, gm. 0.01 to 0.015 (gr. $\frac{1}{6}$–$\frac{1}{4}$), and mercury with chalk, gm. 0.06 to 0.12 (gr. 1 to 2), t. i. d. after food. On completion of the course of arsphenamin and mercury, treatment is continued by a series of fifteen intramuscular injections of mercury given at weekly intervals. For this the salicylate of mercury in a dosage of gm. 0.065 to 0.13 (gr. 1 to 2) is a good selection.

After the twenty-one to twenty-five weeks of treatment, outlined above, have been given the patient is allowed an intermission of four to eight weeks, and then the course of arsphenamin and mercury is repeated. It is sometimes permissible to replace the mercurial injections by the oral administration of the drug.

There may be times when, for certain reasons, it is not deemed possible to treat the patient by the above-mentioned courses of injections. In such cases mercury can at least be administered orally. Satisfactory preparations have been mentioned. As a rule, it would seem that today mercury is rarely prescribed without the precaution of special care of the teeth, but, in addition, it should be emphasized that attention be directed toward the diet. Mercurial preparations often produce diarrhea of such severity that the patient refuses to continue the use of the drug. This can usually be avoided by prescribing a diet which excludes the articles of food known to stimulate bowel action, *i. e.*, fruits, green vegetables, coarse cereals, etc. A normal diet may be resumed if the drug is well tolerated.

Iodid of potassium is probably of use only in the cases coming under treatment years after the initial infection. It may be prescribed in doses of gm. 0.6 to 1.3 (gr. 10–20) t. i. d. after food for alternate two weeks over long periods. Some syphilographers prefer that the amount of the iodid should not exceed the smaller of the doses listed above.

No patient should be dismissed as cured, but advice should be given that he report at six- to twelve-month intervals for re-examination and an opinion as to the need of further treat-

ment. A return of active symptoms or evidence of a progression of the syphilitic lesions, regardless of the Wassermann reaction, should be an indication for the resumption of full treatment.

Treatment may be further discussed according to the type of case.

1. Cases in which the cardiac symptoms are present within a few weeks or months of the primary lesion of syphilis: The patient should be restricted to bed and antiluetic therapy instituted. There appears to be less danger of untoward results if mercury is administered first and followed within two or three weeks by a course of arsphenamin. The patient may be allowed up after treatment has been carried out for two or three weeks and there is evidence of improvement. The further treatment is that described above.

2. Cases coming under treatment years after the primary infection, and exhibiting moderate physical signs with but little evidence of cardiac failure: The courses of arsphenamin, mercury, and potassium iodid, as already outlined, are indicated. If angina pectoris is present the measures (which will not be entered into in this paper) indicated for this condition should be added. The general hygienic treatment recommended for heart disease of other causation should be prescribed.

3. Cases with aneurysm, heart-block, marked symptoms of heart failure, etc: If the heart failure is severe, treatment should first be directed toward its relief. The measures to be employed do not differ from those suitable for the treatment of heart failure of non-syphilitic origin. After some degree of control of the cardiac embarrassment has been obtained treatment against the syphilitic infection should be instituted. It will usually be safer to commence with mercury. After two to three weeks it may be proper to administer arsphenamin, starting as low as 0.05 to 0.1 gm. and not exceeding, perhaps, 0.3 gm. Mercury, in the form of pills or as an inunction, and iodid of potassium have the same indications as described above.

Discussion of the special treatment of aneurysms will not be undertaken in this paper.

ILLUSTRATIVE CASES

A few cases will be cited. The histories and the data from the physical examination will be abbreviated.

Case I.—Married man, fifty-three years, real estate broker, seen in consultation with family physician.

Family History.—Wife and 2 sons living and well. Paternal grandmother and some of his mother's relatives suffered from asthma.

Past History.—Asthma began at two years and has been present off and on until fifteen years ago, when an operation on the nose brought relief. Pneumonia at thirteen and again at seventeen years. At the age of twenty had a chancre with skin eruption, for which internal medication was taken for three years. Gonorrhea at twenty-seven, followed shortly by an arthritis which confined him to bed for two months. No definite recurrence of the arthritis. Four years ago an inflammation of the eye appeared; this was diagnosed as syphilitic by a well-known eye specialist.

Present Illness.—Gradual onset of dyspnea on exertion one and a half years ago. This increased so that eight weeks back he consulted his family physician. Marked edema of the legs noted the past ten days, and for four days he has been forced to remain sitting in a chair because of dyspnea.

Physical Examination.—Orthopneic, visible pulsation of the carotids, face pale, with slight cyanosis of lips, ears, and hands. Heart, impulse in fifth and sixth spaces, extending nearly to anterior axillary line. No thrill. By percussion the right border is 3 cm. from midsternal line and the left 4 cm. outside nipple. No abnormal dulness at base of heart. Loud blowing diastolic murmur audible from second right costal cartilage to apex, maximum along left sternal margin. A systolic murmur at aortic area and transmitted to neck; at apex there is a soft systolic murmur transmitted toward axilla and base. Second sound heard only at base of heart. Action regular. There is a slight impairment of resonance at the base of both lungs, with some medium râles. Pulses equal, rate 54 to 64,

definitely Corrigan in type. A faint capillary pulsation is present. Considerable soft edema of lower legs and in posterior thighs.

A slight improvement followed the restriction of the fluid intake and the free use of digitalis and diuretics, but death occurred ten days later.

Discussion.—This patient was suffering from an enlarged aortic regurgitant heart with cardiac failure, but the diagnosis should not have rested there. The condition was probably an advanced stage of cardiac syphilis, and if at an earlier date (the patient consulted a physician at the time of the eye affection four years before) vigorous antisyphilitic therapy had been instituted it is possible the process might have been checked before the integrity of the heart and aorta was seriously impaired. It is known that true bronchial asthma, as is admitted by Walker,[1] an authority on its specific therapy, does not of itself damage the heart. The arthritis was probably of gonorrheal origin, and if the same infection had attacked the heart it would have done so by producing a form of septic heart disease, which, as is well known, is usually fatal within a relatively short period. Thus, having established the presence of aortic regurgitation, mitral stenosis, or what not, it is an error today not to go further and endeavor to determine its etiology, a recognition of which may be of far greater importance.

Case II.—Boston City Hospital, No. 425866. Man, fifty-three years.

Family History.—Wife living and well, never pregnant.

Past History.—Chancre admitted thirty-five years ago; treatment for nine months. Has had arsphenamin and mercury during the past five weeks. Otherwise recalls no previous illness until five years ago. Has lost 50 pounds in last two years.

Present Illness.—Five years ago was told he had "a bad heart." Since then has had occasional spells of shortness of breath and has been unable to work.

Physical Examination.—Visible pulsation of carotids and

[1] Walker, I. C.: "Bronchial Asthma," Oxford Loose-Leaf Medicine, 1920, Oxford University Press.

other peripheral arteries. Heart, impulse in sixth space almost at midaxilla. Soft systolic murmur at apex with first sound. At aortic area a diastolic murmur replaces the second sound and is well transmitted to left sternal margin. Rhythm is absolutely irregular.

Fig. 253.—Case II. Auricular fibrillation. Heart rate 115 to 125. The larger abscissæ indicate fifths of a second.

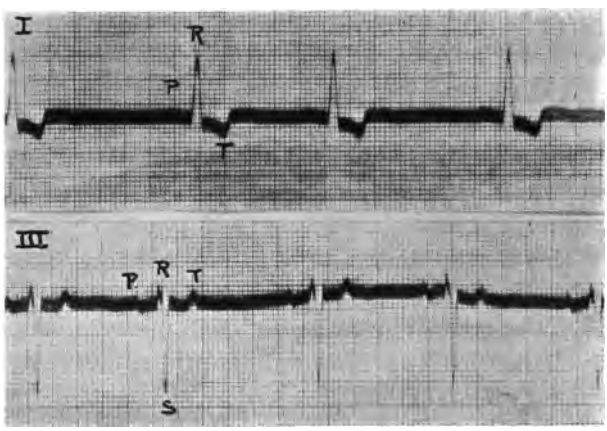


Fig. 254.—Case II. Normal rhythm restored by quinidin. Lead I above and Lead II below to show left ventricular preponderance; index equals +28.5. Rate to 50 to 60, and T wave depressed, both probably due to the free amount of digitalis administered before the quinidin therapy.

Blood-pressure 118/0, and later 128/0. Wassermann reaction strongly positive. The *x*-ray shows an enlarged heart and aorta.

The auricular fibrillation (for such was the arhythmia)

was brought under control by digitalis and subsequently removed by the use of quinidin sulphate. Normal rhythm has persisted to date (three months). Some of the electrocardiograms are appended.

Discussion.—The above is similar to Case No. I, but apparently of slower progression. Attention is called to the presence of auricular fibrillation with a syphilitic heart, a combination which has been doubted by some. The response to quinidin therapy has been most helpful.

Case III.—Boston City Hospital, No. 424996. Man, aged fifty years.

Family History.—Wife living and well; 6 children living and well. There have been no miscarriages.

Past History.—Frequent sore throat of moderate severity; no history of other infections of rheumatic group. Gonorrhea at eighteen; syphilis denied.

Present Illness.—The first symptom was dysphagia, eighteen months ago. Palpitation, dyspnea, and cough past sixteen months, during which time he has been unable to work. For two months has had frequent attacks of "smothering," most marked at night. Swelling of legs past week.

Previous entries to hospital: June, 1920 the Wassermann reaction was negative on both blood and spinal fluid. The *x*-ray showed an enlargement of the aortic shadow suggesting aneurysm. Diagnosis: Aneurysm of the aortic arch and aortic insufficiency. July, 1920 Wassermann reaction strongly positive.

Physical Examination (early in October, 1921).—Left pupil larger than right, both react to light and distance. Slight cyanosis of face. Visible and palpable pulsation in suprasternal notch. Marked throbbing of right carotid; left neither visible nor palpable. Heart, impulse in sixth space well outside nipple line. Supracardiac dulness at first space measures 8.5 cm. There is a loud systolic murmur over the base of the heart and it is well transmitted to neck. Diastolic murmur almost replacing second sound at aortic area and loudest along left sternal margin. At apex there is a systolic murmur with the first sound. Rhythm very irregular, averaging 25 per minute.

Pulse at right wrist is well-marked Corrigan in type; that on left is barely palpable. Liver, lower border palpable 5 cm. below costal margin in right mammary line, upper border at sixth rib. Marked edema of legs and external genitalia.

Roentgen examination demonstrates a fusiform enlargement of the transverse part of the aortic arch.

The electrocardiogram showed heart-block not quite complete, for the ventricular rate varied from a 2 to 1 to 1 to 1 rhythm with the auricle. At times the additional "a" waves could be distinctly seen in the venous pulse of the neck during cardiac diastole.

The severe heart failure continued and death followed early in October, 1921. A limited autopsy was obtained and dis-

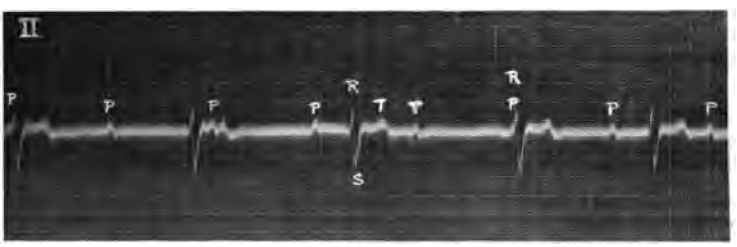


Fig. 255.—Case III. Heart-block. Rate of ventricles, 36; that of auricles, 58 per minute.

closed a large aneurysm of the transverse aortic arch, and this almost obliterated the openings of the left carotid and subclavian arteries. The aortic wall showed advanced syphilitic changes which were continued down to the aortic cusps. The heart was considerably enlarged; except for the fibrous thickening of the aortic valve the valves were normal. Microscopic examination was not made.

Discussion.—The symptoms of this aneurysm began eighteen months before death. The negative Wassermann reactions on both blood and spinal fluid in June, 1920 should be noted. Too many diagnoses of cardiovascular syphilis are discarded because of a negative Wassermann test. It is obvious from the description that this was an advanced case, and relatively hopeless to treat.

Case IV.—Boston City Hospital, No. 429730. Single man, forty-six years, member of fire department.

Chief Complaint.—Daily attacks of pain, starting in right lower jaw and radiating to right neck, arms, and precordia.

Family History.—Unimportant.

Past History.—Never sick except for accidents. In 1911, fall on spine; 1916, fracture of left tibia; 1917, fracture of left olecranon process; 1920, fracture of left clavicle; and in March, 1921, fell through hatchway and fractured right clavicle, right humerus, sternum, and several ribs. Denies venereal disease by name and by symptoms.

Present Illness.—Since March, 1921 (eleven months ago) has had frequent attacks of pain which apparently starts in right lower molar tooth and radiates to neck, shoulder, and arm on the right side, and to the upper precordia. Occasionally the pain radiates to the left shoulder and arm. These attacks follow exertion or the attempt to walk against a cold wind. The pain is severe enough to force the patient to discontinue whatever he is doing and remain motionless. Believes it would be a great effort to speak during the attack. The latter lasts for only about two to five minutes. Is conscious of a distinct lessening of physical power since the attacks began eleven months ago.

Physical Examination.—Teeth appear normal; no tenderness to pressure on right lower molar. Heart, increased supracardiac dulness especially to the right at first intercostal space. Soft systolic murmur at aortic area and transmitted to neck. Blood-pressure 104/76.

x-Ray of teeth shows no pathology. The chest plates show a prominence of the aortic shadow to the right. Width of great vessels 6 cm. The cardiac apex is lowered into the left curve of the diaphragm, and the outline of the lateral wall of the left ventricle is lengthened. Transverse diameter of heart 16 cm.

The Wassermann reaction on two occasions was moderately positive.

The electrocardiogram was normal.

Discussion.—A case of angina pectoris, and at the patient's age, forty-six years, syphilis should be the first thought as the cause. It is true that the point of origin of the pain is atypical, but such occurs and has been described by Sir James Mackenzie in his book on heart disease. The history of the numerous

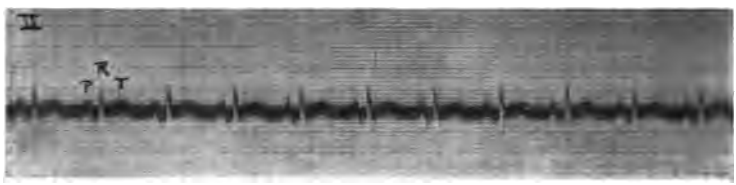


Fig. 256.—Case IV. Normal rhythm, rate 97.

injuries is somewhat confusing, but should not, it would seem, prevent the diagnosis of angina pectoris, probably of luetic origin. The *x*-ray and Wassermann lend some support to this diagnosis. It is extremely important that a therapeutic test of antisyphilitic treatment be instituted without delay. The patient was discharged to his private physician with this advice.

CLINIC OF DR. CHANNING FROTHINGHAM

CLINICAL LECTURE TO THE THIRD YEAR CLASS,
HARVARD MEDICAL SCHOOL, 1922

SYPHILIS

SYPHILIS is an infectious disease produced by the Spirochæta pallida. An attempt to call this spirochete the Treponema pallida has been made, but the name of Spirochæta pallida is so universally used that it probably will become the permanent name for this organism. Although this organism does not produce a very severe febrile reaction or cause marked prostration during its invasion of an individual, some at least of the spirochetes are very resistant to attempts to kill them off after they have once invaded the human host. Although a great number of the Spirochæta pallida may be destroyed quite readily after they have invaded an individual it is exceedingly difficult to remove all of them from the human body. These spirochetes which resist destruction may live an indefinite number of years within the human body, and, therefore, it is important to remember that a person once infected with syphilis may always carry with him for the remainder of his life living spirochetes. Although the point of entry for the spirochetes is usually on the genitalia and the transference from one individual to another usually occurs at the time of sexual intercourse, the spirochetes may invade an individual at any point which comes in sufficient contact in any manner with the living organism or they may be transmitted to an individual before birth from an infected mother.

In order to understand this disease properly it seems desirable to give up the old nomenclature of primary, secondary, and tertiary syphilis and look upon syphilis as an infection with the Spirochæta pallida in which the organisms may be locally or generally distributed throughout the body. The infection takes

place at some one point on the body, but already by the time that the spirochetes have produced a local lesion which can be diagnosed they have spread from the initial lesion so that excision of it will not eradicate the disease. Soon after the spirochetes gain access to the body they multiply rapidly and distribute themselves generally throughout the body. They produce lesions at this stage, especially in the skin and on the mucous membranes. Following this general distribution of the spirochetes throughout the body they then begin to diminish in numbers. Whether this is because of some antibody formed by the human host which kills them off or because their life has run out and they die off is not definitely established. It is possible that all the spirochetes may be destroyed at this time, but certainly in the great majority of cases this does not occur. Some at least remain alive in an organ or other parts of the body. These spirochetes tucked off in some part of the body may survive without producing any disturbance for many years or they may be slowly producing some lesion through their activity which will not cause any symptoms for some years. These quiescent spirochetes may at any time become active, and in addition to causing disturbance locally they may in some instances multiply and again distribute themselves fairly generally throughout the body. During the early stages when the spirochetes are generally distributed throughout the body no serious permanent damage is, as a rule, done to the various organs and tissues of the body with the possible exception of the arteries. In the instances in which the spirochetes have remained active over a period of years definite permanent injury to the tissues may take place. This is especially true in the central nervous system and in the vascular system. The importance of these permanent injuries to the tissues rests in the fact that although eventually the spirochetes in these local areas may be killed off, the end-result from the lesions produced by the spirochetes may be sufficient to cause death or incurable disease.

In making a diagnosis of syphilis it must be realized that the disease may have been recently acquired or it may have existed

in the individual for a period of years. The symptoms in the two instances are quite different, because in one instance they are the result of spirochetes localized in one point on the skin or generally distributed throughout the body, and in the other instance they are the result of spirochetes which have lived locally in some part of the body for years. The diagnosis of syphilis depends upon the physical signs or upon laboratory findings. The physical appearance of the initial lesion or point of entry of the spirochetes into the body you will see in your course on syphilis and therefore no time will be spent in its description in this lecture. The various types of skin lesions which are the result of a general distribution of the spirochetes throughout the system will also be shown to you in your course on syphilis or in your work in dermatology. Lesions of the mucous membranes, general glandular enlargement, and falling of the hair will also be demonstrated to you in these courses.

The great majority of cases of syphilis in the early stage of the disease are recognized from the character of the lesion at the initial point of entry or the various types of skin eruptions. In some instances the lesion at the point of entry may not be characteristic, as cases of definite syphilis are met in persons who have given a history of only having had a so-called soft, non-syphilitic chancre. Occasionally, especially in women, the initial lesion is not found, the eruptions of the skin are absent or overlooked, and the disease only manifests itself by general symptoms, such as headache, general malaise, etc. In these instances the disease cannot be diagnosed simply from physical examination and recourse must be had to the assistance offered by the laboratory.

In the cases in which the general distribution of the spirochetes has gone by and the lesions are simply those produced by the few spirochetes remaining in some local situation the physical signs are quite different. In these later stages of the disease which may come on from some months to many years afterward one finds in the skin ulcerative and destructive lesions if the organisms survive in this tissue. Occasionally the spiro-

chetes apparently again increase in numbers and become distributed generally in the system so that a fairly diffuse skin eruption takes place. This is unusual in the late stages. The prolonged local activity of the spirochetes may lead to lesions in practically any organ of the body, and therefore in this talk it would be entirely too comprehensive to endeavor to give the symptoms resulting from these lesions. Some of the lesions produced will simply be mentioned so that it may be appreciated what a diversity of symptoms may result from the localized action of the spirochetes after they have been within the body for some time. On the part of the central nervous system meningitis, tabes dorsalis, general paresis, or gumma may occur. In addition, vascular lesions in the brain itself may produce destruction of the brain tissue with resulting varieties of paralysis. Atrophy of the optic or auditory nerves with resulting blindness and deafness are met. Inflammation of the iris of the eye or infiltration of the cornea may occur. The spirochetes may produce destruction of bone and cartilage or proliforation with subsequent necrosis of the periosteum. This may occur anywhere in the body. Gummatous lesions may occur anywhere in the tissues of the body. This gumma consists in necrosis of tissues probably dependent upon vascular lesions whereby the blood-supply to the part is destroyed and necrosis takes place. A lesion of especial importance in the vascular system is seen in the destruction of the muscle-fibers and elastic tissue of the medial wall in the aorta. If this destruction is confluent in a big enough area aneurysm will result. If it is more unevenly distributed a general dilatation of the aorta without actual aneurysm may take place. This process often extends down to and involves the aortic valve with resulting regurgitation through the aortic valve and subsequent giving way of the heart muscle as a result of this valvular defect. Lesions of the heart muscle itself occur, probably as a result of lesions in the vessels supplying the muscle. Aneurysms, of course, may occur in any other artery of the body. Gummatous lesions occur in the liver and testicles. They have been reported in almost all organs, but in the other organs of the body they are more rare.

From the above it is evident that, as a result of the activity of the spirochetes in local parts of the body over some time, serious damage may occur to almost any tissue in the body with a set of symptoms resulting from the injury produced. This set of symptoms may be entirely cleared up by overcoming the activity of the spirochetes, but in other cases even after the acute process has subsided and scar tissue formed definite symptoms pointing to disease of the organ involved may continue as a result of the injury done. Therefore, although the syphilis is cured the end-result of the syphilis may lead to a permanent group of symptoms, or even death. So much for the diagnosis of syphilis by physical examination and history of the case.

Within recent years the diagnosis of syphilis by laboratory procedure has received a tremendous impetus, due to the discovery of the spirochetes, the so-called Wassermann serum reaction, and the examination of the spinal fluid by various procedures. By means of special illuminating and staining methods the Spirochæta pallida may be recognized by trained observers under the microscope and it may be recovered from the initial chancre or from the neighboring glands by puncture early in the course of the disease. The Wassermann reaction in the blood-serum, although specific to a great extent for syphilis, is not absolutely so, and experience has taught us that a final decision in regard to the presence or absence of syphilis cannot rest wholly upon this reaction. In regard to the Wassermann reaction in the blood it must also be remembered that it does not become positive as soon as the signs of the disease become manifest, and therefore the infection may become well established in an individual before the diagnosis can be determined by this test. Furthermore, in certain cases in which the disease has existed for some time within an individual the Wassermann reaction may be negative and still the disease active. Also it sometimes happens that a negative Wassermann reaction in the blood may become positive after a small amount of antisyphilitic treatment in cases with syphilis of long standing. It is evident, therefore, that syphilis may be active without a positive blood

Wassermann, and, on the other hand, there are a certain number of diseases other than syphilis in which the blood Wassermann is positive. Prominent among these are leprosy, jaundice from any cause, and various of the acute febrile conditions during the acute stage.

Examination of the cerebrospinal fluid for syphilis consists in counting the cells, testing for the presence of globulin, performing the Wassermann reaction upon a certain amount of the spinal fluid, and carrying out a test with a colloidal gold solution. On account of the expense the colloidal gold test is not in general use, but seems to be of considerable value in detecting the type of syphilitic infection in the central nervous system, as there is a rather characteristic response to this test in general paresis. In syphilitic disease of the central nervous system the cell count is usually elevated in the cerebrospinal fluid, the globulin test is usually positive, the Wassermann reaction should be positive when 2 c.c. or less of the cerebrospinal fluid is used. If the Wassermann reaction is negative when 2 c.c. of the cerebrospinal fluid is used it is considered sufficient, as a positive reaction may occur with larger amounts of the cerebrospinal fluid when no syphilis is present. In the cerebrospinal fluid the occurrence of a positive reaction without syphilis is apparently less frequent so far as the Wassermann reaction is concerned than in the examination of the blood, but in certain inflammatory conditions of the meninges the Wassermann reaction may be positive when syphilis is not present.

It is important to remember that the blood and spinal fluid do not necessarily react the same in an individual case to the Wassermann reaction. For in many instances the cerebrospinal fluid remains negative when the blood is positive. On the other hand, in certain cases the cerebrospinal fluid may show the signs of active syphilis in the central nervous system and yet the Wassermann reaction in the blood-serum may remain negative.

As the collection of the blood for the Wassermann reaction in the serum is a simple procedure this test for the diagnosis of syphilis should be employed freely in the handling of a case. As the collection of the spinal fluid is a more complicated pro-

cedure it is important to decide under what circumstances this test should be performed. Since in the early course of the disease the spirochetes are generally distributed throughout the body it is presumable that in many cases the cerebrospinal fluid at this stage of the disease will be positive. As no change in the method of treatment will probably be instituted for a patient in the early stages of syphilis on account of a positive spinal fluid at this stage of the disease, there is no practical value in studying the spinal fluid early in the course of syphilis. In certain rare cases early in the disease, even in the presence of active treatment, symptoms referable to the central nervous system appear and continue. In such cases examination of the spinal fluid is important, and if the symptoms persist and the spinal fluid gives a positive reaction for syphilis, intraspinal treatment may be instituted. On the other hand, the study of the spinal fluid should be carried out on all cases of syphilis which have been recognized and treated early in the course of the infection when it becomes time to discharge the patient in order to make sure that the spinal fluid is also negative.

The problem is different, however, in the cases of syphilis which are met with late in the course of the disease, after the general distribution of the spirochetes throughout the body has been overcome and there are only a few local areas in which the spirochetes are still active. For in these cases the spirochetes may still live in the central nervous system, and if these spirochetes are active in the central nervous system some years after the original infection it is important that intraspinal treatment, in addition to other methods; be instituted promptly in order to avoid further destruction of nerve tissue and the development of serious disorders of the central nervous system, such as general paresis or tabes. Frequently in cases in which the spirochetes are still active in the central nervous system and have been for a considerable number of years no symptoms will be found on routine examination of the patient referable to the central nervous system. Therefore, it is an excellent rule in cases of syphilis in which the infection has existed for some years to study the spinal fluid before instituting treatment. Of course, in these

cases also the cerebrospinal fluid should be again examined before pronouncing the patient ready for discharge.

The successful treatment of syphilis is a difficult problem, because it takes a long time to eradicate all the spirochetes from the body, and treatment must be continued by the patient long after he feels well and is free from symptoms. The examples of unsuccessful and incomplete treatment of this disease are all too numerous. No matter at what stage of the disease one first meets the patient, treatment should be instituted to accomplish two definite objects. The first is to clear up any symptoms referable to activity of the spirochetes, and the second is to clear up any laboratory evidences of activity of the spirochetes in the blood or the cerebrospinal fluid. It must be remembered that it will be impossible by antisyphilitic treatment to clear up the symptoms referable to the scars produced by the activity of spirochetes in various organs in the past, and the judgment of the pratitioner is nececsary in these cases to decide which symptoms are due to the activity of the spirochetes and which are due to the end-results of their activity. It is frequently a difficult matter to decide whether any spirochete activity is still going on in a limited number of cases.

It is usually possible by proper treatment to clear up the symptoms due to the activity of the spirochetes. It is more difficult and sometimes impossible, especially in cases in which the infection has been going on for some time, to clear up the laboratory evidence of active syphilis. It must be remembered that, although following treatment the laboratory evidence of syphilis may be negative, it may become positive again later after the discontinuance of treatment. It is important before treating the patient to explain to him what you are trying to do, and that in order to do this it will probably mean attention to the treatment on his part for a period of months or years rather than for just weeks and months. It must also be explained to him that this treatment is expensive, and, therefore, if he cannot afford to take the treatment as a private patient provision should be made for him to take it in some of the charitable institutions. One meets so many instances of people who start

off taking treatment as a private patient until their money is used up and then stop treatment, while if it had been made clear to them that the whole process was going to take considerable time and money they might have made different arrangements for the treatment so that it could have been carried through to its proper conclusion.

There is no definite amount of treatment which will definitely clear up the disease in an individual patient. The amount of treatment necessary to eradicate the disease varies tremendously in different cases. The best way is to have a definite amount of treatment which one looks upon as a block of treatment, to give that to the patient, and then to see what the results of that treatment are, so far as symptoms and laboratory tests are concerned. The number of times it will be necessary to repeat the block of treatment after a rest period will depend upon the results obtained.

The medication used in the treatment of syphilis is some preparation of arsenic, such as salvarsan, diarsenol, etc., which should be given intravenously; some preparation of mercury which should be given intramuscularly, but which may be given less effectively by inunctions through the skin or by mouth. The activity of these substances against the spirochetes is thought to be increased in some instances by the administration of iodid by mouth, usually in the form of potassium iodid. In addition, in those cases in which it is advisable to institute treatment intraspinally, serum which has been collected from a patient to whom a dose of salvarsan had been given a short time before is fortified with minute doses of salvarsan and given into the spinal canal after drawing off a certain amount of the cerebrospinal fluid. The amount of intravenous and intramuscular treatment which should constitute a block of treatment will vary with the preparation used and with the judgment of those directing the various clinics. The amount of intraspinal treatment thought necessary to use in cases in which intraspinal treatment is indicated also varies with the individual case. In some clinics the value of the intraspinal treatment is still doubted, but in the majority of those clinics in

which it has been given a fair test it is looked upon as being a valuable asset for treating cerebrospinal syphilis. At the Peter Bent Brigham Hospital a block of intravenous and intramuscular treatment consists in six injections of diarsenol given at weekly intervals. The injections consist of 0.3 or 0.4 gram each week. The mercury preparation used is the soluble mercury succinimid which is given twice a week for eighteen doses. The mercury and diarsenol may be given at the same time. The first six doses of the mercury are 0.013 gram, the second six 0.026 gram, and the third six 0.039 gram. The intraspinal injections are usually given every two weeks. At the time of the intraspinal injection an intravenous injection is also given, and an intravenous injection is also given on the week between the intraspinal therapy.

Modifications in the dosage and time of administration must be made to fit the problems presented by the individual case, but in each instance treatment should be kept up so long as any symptoms referable to activity of the spirochetes persist, and a persistent effort should be made to make the Wassermann test in the blood-serum permanently negative and the spinal fluid normal to laboratory tests.

CLINIC OF DR. JAMES P. O'HARE

PETER BENT BRIGHAM HOSPITAL

COMMON SENSE IN THE INTERPRETATION OF HYPERTENSION

THE most popular medical "disease" of the present time is, without any question, "high blood-pressure." The medical literature is full of it. The advertising columns of our medical magazines abound in preparations of iodid or nitrites or this or that "sure cure" for hypertension. The popular magazines are running—very unfortunately, I think—articles which acquaint the eagerly curious public with all the possible accidents from increased pressure. Ladies at their sewing guilds or bridge parties gossip about their pressures and their diets. When they come to your office they can hardly wait until you take the stethoscope out of your ears after taking the pressure before they want to know "What is it today, doctor?" If they are told that it is 10 points lower, they are so pleased, whereas if it is 10 points higher, they are the picture of gloom. And, if you sanely refuse to tell them what their pressure is, they coax you with, "Knowing my pressure never bothers me, doctor." It is the old story of a little knowledge being a dangerous thing.

Now, we, as physicians, are largely responsible for the dangerous character of this "little knowledge." Too often do we regard hypertension as a disease in itself. Too often is our opinion of a patient based on a single blood-pressure reading. Too much do we discuss blood-pressure with our patients. The sum total of real knowledge of hypertension is very small and there is much false knowledge and half-truth. What do we truly know about high blood-pressure? We know that it most

often occurs at middle life or beyond, chiefly in those hard workers with a family history of vascular disease. We know that it may be associated with kidney trouble or it may be part of the syndrome called vascular hypertension. In all probability the majority of our cases of chronic nephritis with hypertension occurring after forty are secondary to an antecedent vascular hypertension. Other phases of this latter disease include angina pectoris, myocardial insufficiency, cerebral hemorrhage, possibly diabetes, etc. Most cases of high blood-pressure die of apoplexy or angina; some die in uremia. We know—and this is not entirely a blessing—that we can measure blood-pressure with a fair degree of accuracy. The simplification and popularization of the blood-pressure machine has made us lean far too heavily on it. It is a fact in medicine that whenever we can measure our patients and record the result in mathematic terms, whether it is blood-pressure, renal function, vital capacity, or anything else, we are more than likely to stress the mathematic result and forget the rest of the patient. We forget, too, that that mathematic result is not always a constant, but more often a variable.

My object today is to demonstrate to you on the screen some of the variations in pressure which are so common in the hypertensive case. In this way I hope to counteract the effect of the senseless interpretation of blood-pressure or the effect of therapy. A study of these will show that we should be extremely cautious in our interpretation of the prognostic meaning of a given pressure level, and that we should be very conservative in judging the value of any therapeutic agent or maneuver on blood-pressure.

The method for taking the blood-pressure, commonly used by house officers and doctors in general, is to slap on the cuff, drive up the pressure in the latter to a point often far above the systolic pressure, and then fairly slowly to allow the mercury to fall until the systolic and diastolic pressure can be read in the usual way. Such a maneuver as this, in its very cruelty, may cause complications which tend to diminish the value of the reading. In a normal person the mere taking of the pres-

sure is nerve-stimulating enough to cause a temporary rise in the systolic pressure. Add to this the effect of pain caused by the sudden and often unnecessary tightening of the cuff, and you can imagine the result. Now, the hypertensive patient is definitely more sensitive. He is much more susceptible to nervous stimulation, and hence, effects seen in the normal are greatly exaggerated. Furthermore, the hypertensive case, at least when I see him, is so well trained in the knowledge of blood-pressure that the very words "blood-pressure" cause an increased tension.

It is my practice to make three successive readings in all cases and to accept the lowest systolic and the lowest diastolic in these three as the fairest. Sometimes it is well to apply the cuff and then allow the patient to rest quietly for fifteen to twenty minutes before making a reading.

Chart 1 illustrates clearly the variations that take place in successive readings. In each column the readings were made as fast as could reasonably be done, allowing between each only sufficient time for the circulation in the arm to re-establish itself, at most not more than three to four minutes. Note the results. In patient *A*, in the first three readings there was a drop of 24 mm. systolic pressure as the patient adjusted herself to the maneuver. In the second column on another day this same patient showed a similar quantitative drop from 204 to 180 mm. In the third and fourth columns a somewhat different curve is shown, illustrating the attitude of the patient at the moment each reading was made. Patient *R* in the last column shows a drop of 28 mm. systolic pressure between the first and last readings. You have observed, of course, that the diastolic pressure does not vary much, but even it may vary quite markedly. Drops in systolic pressure of 20 to 30 mm. like these are not at all unusual, and at times the fall may be even greater. Now, is it fair for us to assume that the patient's average pressure during the day is represented by his high figures 192, 204, 232? It seems to me that it must be much nearer our low figures, 168, 180, 204. No doubt at times he is nervously stimulated by various events, so that at those moments

the pressure is higher. But I think you will all agree that the low level figures more nearly represent the average pressure, could we have a continuous record. This chart, therefore, shows

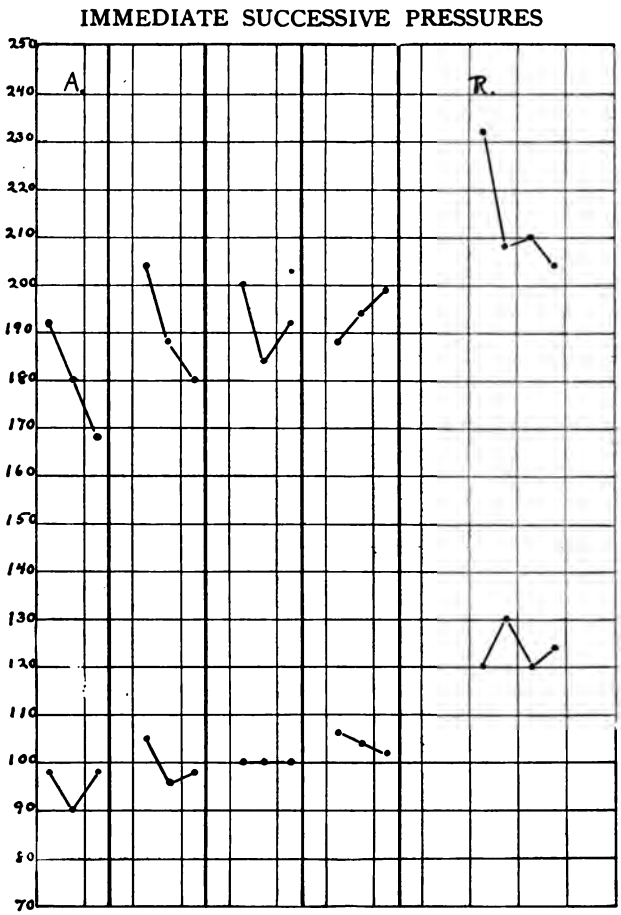


Fig. 257.—Chart 1: Immediate successive pressures on 2 patients, *A* and *R*. On *A* are four curves made on different days.

how great variations may take place from moment to moment. It certainly suggests the desirability of making three readings. How senseless it is to say the patient's pressure was reduced 10 to 20 points by a diet or a drug!

Chart 2 shows the effect of some of these various stimuli occurring during the day. This patient was put to bed in a

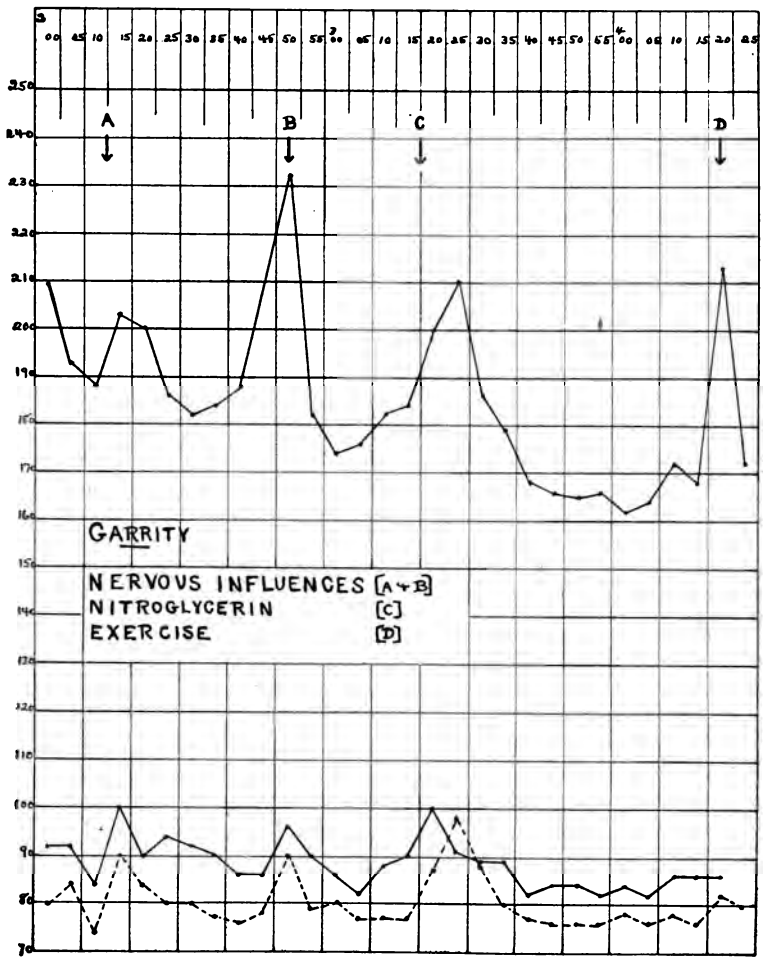


Fig. 258.—Chart 2: Effect of various stimuli on hypertensive patient. At top of chart is the time when readings were made. The uppermost curve represents the systolic pressure, the middle curve the diastolic pressure, and the lowest curve the pulse-rate. *A*, *B*, *C*, *D* are explained in the text.

quiet room, and after a preliminary adjustment period of twenty minutes readings were taken every five minutes for two hours.

and twenty-five minutes. The upper line is the systolic pressure. The next line is the diastolic and the broken line at the bottom the pulse-rate. Let us omit peak *C* (effect of nitroglycerin) temporarily and note the other variations. The usual curve obtained in this experiment is a fall in the course of the first half-hour of 20 to 30 mm. to the base line, from which it arises only as a result of stimulation. What, then, is the explanation for the enormous variations in the systolic pres-

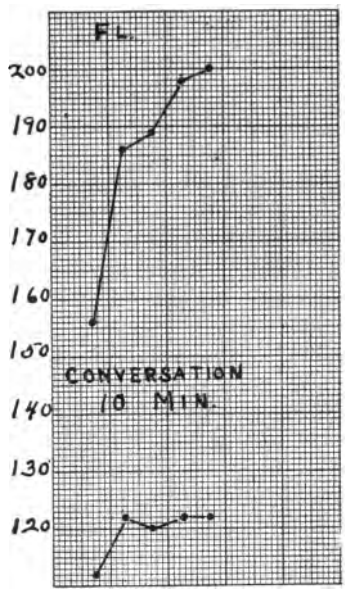


Fig. 259.—Chart 3: Effect of conversation. Readings made every two minutes.

sure shown in this chart? The first rise *A* is due to a very simple stimulus. In this case the patient's chest was somewhat exposed, and to avoid the effect of cold in the latter part of the experiment the nurse pulled up the blanket which had been over the lower part of the body. The result was a rise of 15 mm. in the systolic pressure and 16 mm. in the diastolic. The sharp rise of 44 mm. at *B* is the result of asking a divorced woman where her husband was. The same rise has taken place in these cases by merely asking the patient what his pressure

was when he first came to the hospital. Peak *C* we will consider later. It is the effect of nitroglycerin. Peak *D* illustrates the effect of exercise—ten pull-ups in bed. Stimuli similar to those of *A*, *B*, and *D* must be fairly frequent during the daily life of these patients. How easy it is to grossly misjudge the patient's condition if we happened to make a single reading

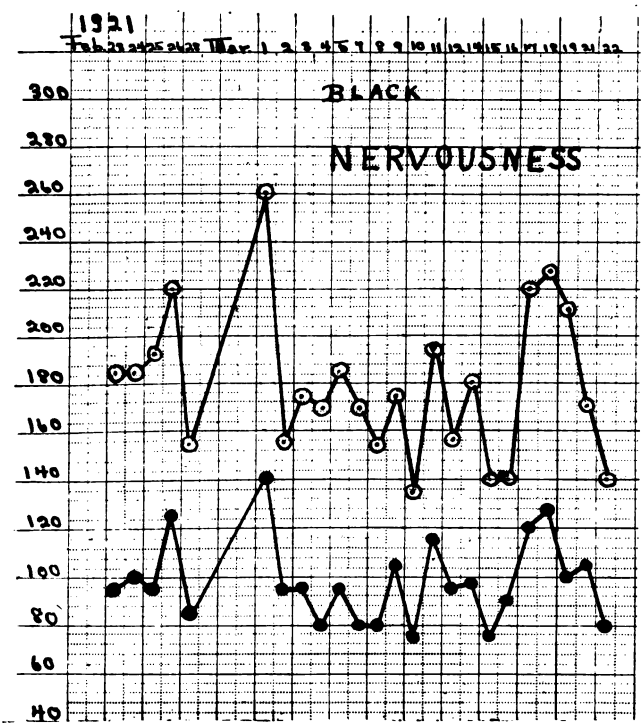


Fig. 260.—Chart 4: Irregular type of curve in a nervous woman. Note the great variations from day to day.

at a time when something has disturbed her! What a different impression is conveyed by a pressure of 232 mm. and one of 174 mm.

Chart 3 illustrates the effect of ten minutes' ordinary conversation in a hypertensive patient. Note the 44 mm. rise.

The mental attitude of the patient at the time the pressure is taken or the kind of day she is having has a very great

influence on the reading we obtain. In Chart 4 is shown the variations that take place from day to day in a nervous woman. She was under constant conditions of rest in bed with fixed intake of water, salt, and protein. A mere glance at the wide swings from a maximum of 260 to a minimum of 138 emphasizes the point I made above that a very erroneous impression of the case is obtained if we happen to take the pressure at a moment or on a day, like March 1st, when the patient is mentally much perturbed, 260 mm. certainly calls up in my mind a very different picture than 138 or 170. Incidentally, this patient was at this time on the diet containing less than 0.5 gm. of salt which Allen has suggested for the reduction of blood-pressure. There has certainly been no evidence in this case to support the dictum that this very low salt intake has been hypotensive.

You have seen in the previous charts the variations in pressure taking place from minute to minute and from day to day. Chart 5 illustrates variations that take place over months and years. As far as we could see there was essentially no change, no cardiac weakening, in this robust, healthy old man from 1914 till the spring of 1921. And yet, look at the variations in his pressure from 235 in 1915 to 146 in 1919. I wonder what sort of prognosis was given him in 1915. I am sure that no one expected him to live seven years, and I do not believe that anyone dared hope that the pressure would ever be near to normal. In the near future I think we will be able to give the answer to such changes and perhaps be better able to prognose such cases. In the meantime we should be extremely cautious in predicting length of life from the height of the pressure at a given time. Other factors, such as the condition of the heart, the arteries, etc., are much more important.

I want you to bear in mind the wide variations you have seen in the previous charts. I want you to remember that fluctuations of 20 to 30 mm. systolic are common and due chiefly to the changes in the mental state of the patient at the time the pressure is taken and that they do not mean much. With this in mind, I am sure you will be more conservative in judging the value of any drug or diet which is said to be of

value in reducing high blood-pressure. The one efficient method of lowering the pressure is to give the patient mental and physical rest.

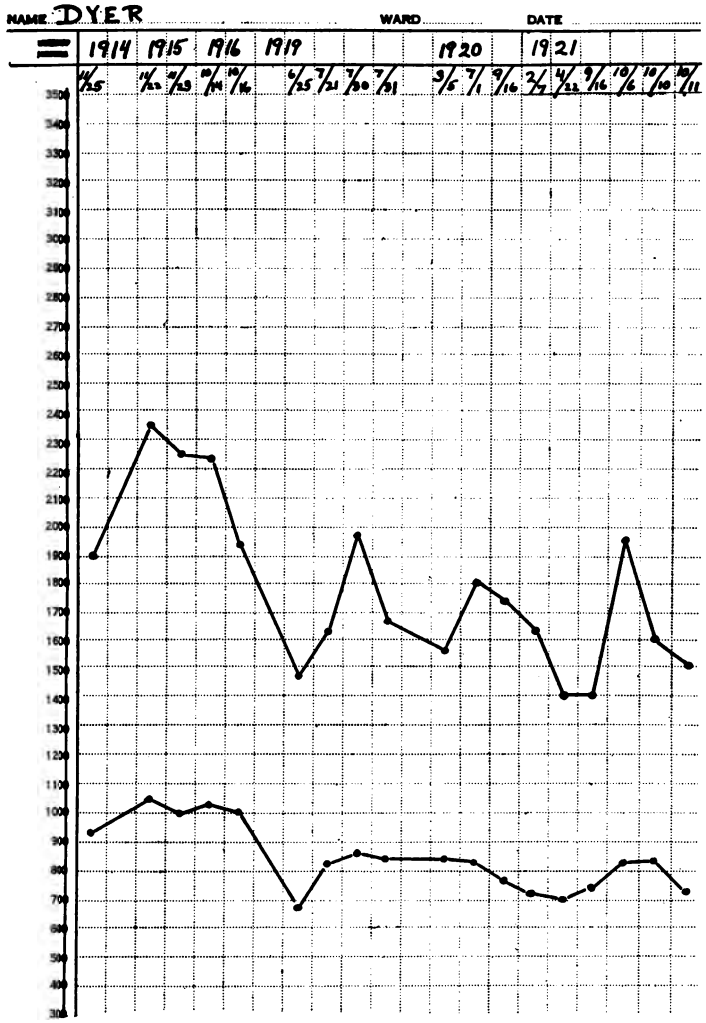


Fig. 261.—Chart 5: Variations in pressure over years.

Let me show you in the next chart (Fig. 262) just what that and that alone may accomplish. The first two curves are from

one patient who was put to bed and given no other special treatment. House diet without restriction of salt or anything else was allowed. I think it is fair to attribute the result to mental and physical rest. Note the changes. In the first curve a drop of 42 mm. systolic and 48 mm. diastolic pressure has

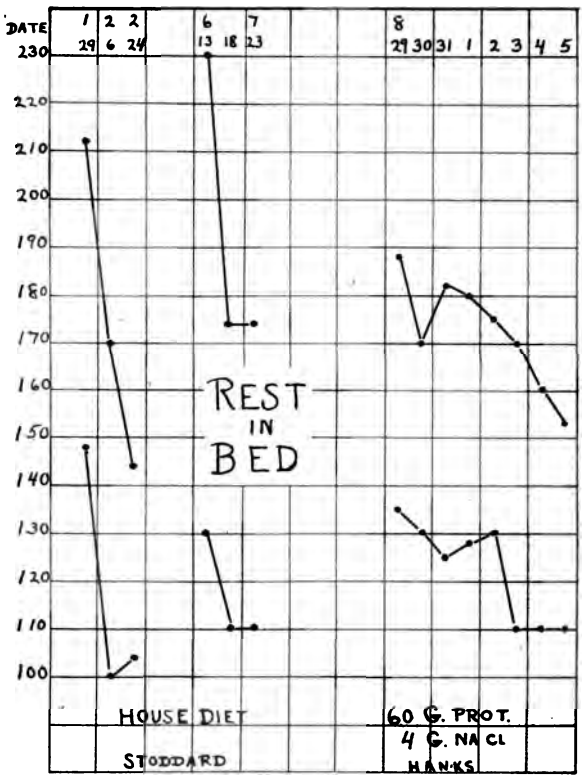


Fig. 262.—Chart 6: Effect of rest in bed. The figures in the top line represent the months and those in the next line the days.

taken place in eight days, and a total drop of 68 mm. systolic pressure in less than a month. In the second curve there is a drop of 56 mm. systolic and 20 mm. diastolic pressure in five days. The third curve illustrates the same thing with daily pressure readings. Note the drop from 188 to 153 mm. systolic and from 135 to 110 mm. diastolic pressure in one week. This

is due alone, I believe, to the rest in bed. As a matter of fact, this is part of an experiment on the effect of lowering the salt intake. In spite of the fact that this patient was getting 4 gm. of salt (twice as much as we ordinarily give such patients) his pressure dropped as indicated. Curiously enough, when the

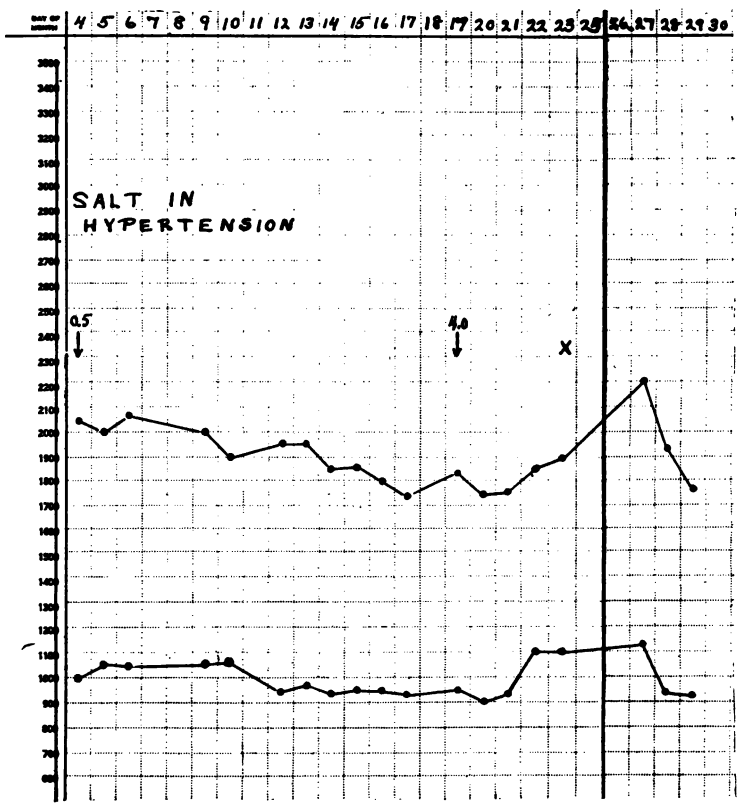


Fig. 263.—Chart 7: At × the patient was disturbed by the comment of the visiting physician. (See text.)

chlorid in his diet was lowered to 0.5 gm., his pressure rose again, due, of course, not to the salt, but to other influences.

Let me say again, in the large majority of patients with hypertension a fall in pressure is due to the physical rest imposed and mental ease obtained rather than to any given drug or therapeutic measure.

Let me show you in the next chart (Fig. 263) how easy it is to be led astray in our interpretation of the effect of therapy. This illustrates an experiment on the effect of low and "high" salt intake. The 0.5 gm. régime was continued up to December 19th, with a fall from 205 to 174 mm. systolic pressure. On that day the 4 gm. régime was instituted, and shortly afterward the pressure rose to well above where it was at the beginning of the experiment. This, at first sight, would seem to be a case for the "low salt" theory. But note the fact that while

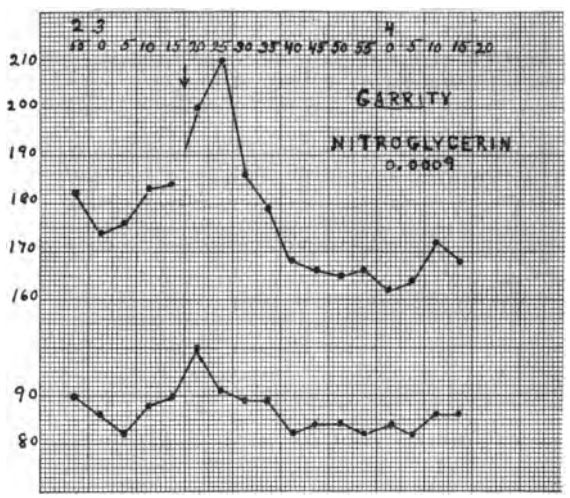


Fig. 264.—Chart 8: Effect of nitroglycerin. Drug given under the tongue at the arrow.

still on the "high" salt intake, the pressure fell again to its former level. (It is only fair to say that it has gone up slightly since.) The chief explanation for this rise is rather interesting. On December 23d the physician making ward "rounds" rather casually remarked that this patient's cardiac pain might be helped by a little digitalis. It so happened that before coming to the hospital a relative of the patient had been discussing, "very knowingly," a high blood-pressure case that had recently died. She told our patient that "It didn't matter how high your pressure was. When, however, they began to give you

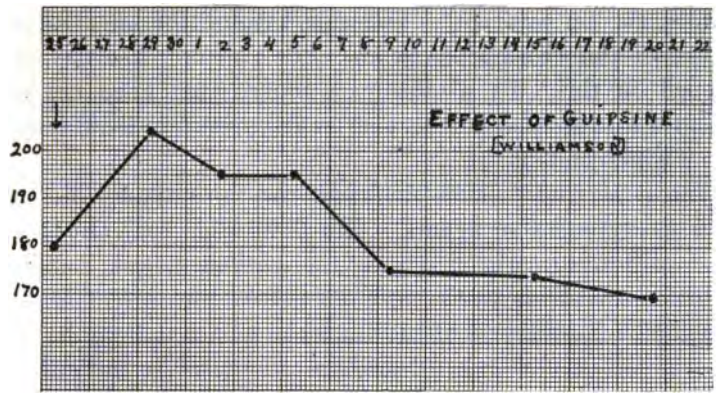


Fig. 265.—Chart 9: Effect of guipsine. This chart is taken from an article by Williamson. The drug was given daily, beginning at the arrow No control period was given. To credit the guipsine with a drop of 10 mm. in pressure in twenty-five days is ridiculous.

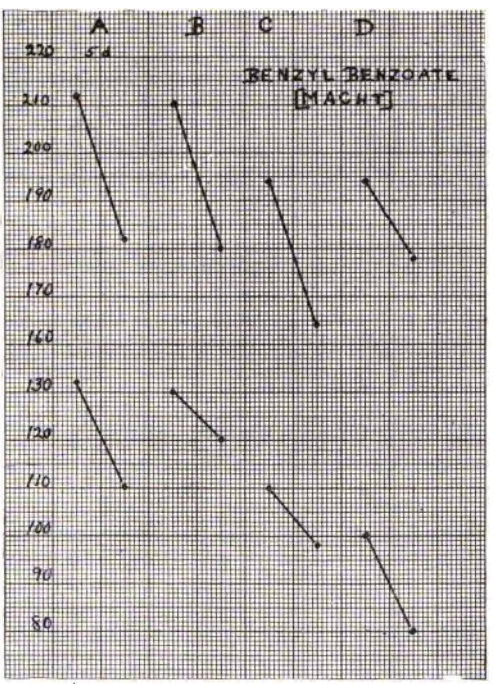


Fig. 266.—Chart 10: Effect of benzyl benzoate. This chart is taken from Macht's article on Benzyl Benzoate.

digitalis the jig was up." You can imagine the effect of the remark of the visiting physician. For two or three days she brooded on this. By accident we found what ailed her and reassurance was followed by a drop in pressure. How easy it is to misinterpret!

The next three charts illustrate the false claims of three drugs as hypotensive agents. The first (Fig. 264) shows the effect of nitroglycerin given to the patient whose complete chart you saw earlier. The drop in systolic pressure of 12 mm. is negligible. (Bear in mind the tremendous falls from rest alone, noted in Fig. 262.) Furthermore, while the patient was having all the symptoms of vasodilation the pressure was higher than in the control period. The drop in pressure occurred after the symptomatic effect had disappeared.

Next (Fig. 265) note the insignificant fall in pressure from the French preparation of guipsine. Certainly 10 mm. in twenty-five days is unimportant.

The last (Fig. 266) shows a similar unimportant drop attributed to benzyl benzoate by Macht in his article on this drug in hypertension. Surely, in view of our findings illustrated in Fig. 262, it is hardly fair to attribute such small drops as those in Fig. 266 to benzyl benzoate.

CONCLUSIONS

1. Take your pressure readings three times.

2. Make observations on the pressure at intervals before you draw any conclusions from it.

3. Let your conclusions be the result of a careful general study of your patient and his pressure. Let them be conservative.

4. Be cautious in attributing to any drug or diet an effect which is probably due to ease of mind and rest of body. As yet yet there is no therapeutic measure that uniformly does as much to reduce pressure as mental and physical rest.

5. Above all, do not discuss the height of the blood-pressure with the patient.

CLINC OF DR. CHARLES W. McCLURE

EVANS MEMORIAL

DIAGNOSIS AND TREATMENT OF PEPTIC ULCER, BASED UPON CLINICAL EXPERIENCE AND EXPERIMENTAL OBSERVATIONS ON PATIENTS

THERE is, perhaps, no field in medicine more burdened with unproved theories than that of diseases of the gastro-intestinal tract. There are obvious reasons for this. In the first place, the extent to which patients in the past could be investigated was often necessarily so limited that but comparatively little has been accomplished in many phases of the field in question. Furthermore, animal experimentation is very difficultly applicable to many phases of pathologic gastro-intestinal conditions in man due to many differences between man and animal, including differences in the nervous constitution of the lower animals as contrasted to that of man. As a result of these factors there is frequently a lack of knowledge (1) of the etiologic factors of gastro-intestinal diseases and (2) of their pathologic physiology. For these reasons there exists a great diversity of opinion regarding the question of the predisposing factors, the etiology, the basis for diagnosis, and the proper treatment of most abnormal gastro-intestinal conditions, each opinion depending upon the personal theories (one might almost say idiosyncrasies) of each writer on the subject. In this connection it may be stated that it seems morally wrong, except in rare cases, to base either diagnosis or therapy upon largely theoretic considerations or upon methods whose efficacy has not been demonstrated by carefully controlled experimental and clinical observations. For these reasons it is advocated that, as regards disturbances of the gastro-intestinal tract, the practice of medicine be strictly limited to the clinical entities and to the methods of treatment which

properly controlled clinical and experimental work have proved to be truly beneficial to patients.

In order to manage intelligently a gastro-intestinal case thorough knowledge of certain essentials is necessary. Of prime importance is the clear understanding of the etiologic factors, in so far as they are known, and of the clinical entities into which gastro-intestinal conditions may fall. In adopting a classification of gastro-intestinal conditions it is of prime importance that the classification afford a basis for the development of a rational therapy for each condition. A classification which will usually suffice for this purpose is as follows: (1) The group in which gastro-intestinal symptoms are due to primary organic disease of the alimentary canal, such as benign ulceration, cancer, tuberculosis, etc.; (2) the group in which gastro-intestinal symptoms are secondary to some definite organic disease outside the alimentary canal, such as renal disease, cardiac disease, pulmonary disease, constitutional diseases, pelvic diseases, etc.; (3) the group in which patients are rendered toxic by the introduction into the system of poisons, such as lead, mercury, etc.; (4) the group of so-called functional gastro-intestinal conditions; and (5) certain rare, serious conditions with predominating gastro-intestinal symptoms, for which no definite cause can be found and the symptoms of which simulate those of organic disease.

The etiologic factors in the above classification are self-explanatory except perhaps for the so-called functional conditions. Concerning the actual cause or causes for these conditions there is much controversy. But so far this controversy has not aided much in relieving patients of their unpleasant gastro-intestinal symptoms. For this reason the author made a clinical study of the functional gastro-intestinal conditions. As a result of this study it was found that the modification of various individual factors, affecting the lives of patients, would lead to relief of symptoms in most cases. A résumé of the greater part of this study will be found in Medical Clinics of North America, May, 1921, Vol. IV, No. 6, p. 1693.

The diagnosis of an abdominal condition, as difficult as it always is, has become unduly complex due to the use of various

laboratory procedures, some of which have been advocated long enough to have crept into text-books and systems of medicine. There is a tendency for more laboratory than clinical judgment to be used in present-day diagnosis, often to the detriment of both diagnosis and the patient. That this statement is not the result of undue prejudice against laboratory procedures is evidenced by the fact that the author of this article is actively engaged in the laboratory as well as the clinical side of medicine.

From the foregoing discussion it may be gleaned that (1) almost any pathologic or functional condition may be accompanied by gastro-intestinal symptoms, and (2) that clinical judgment is of the utmost importance in the diagnosis. Bearing these two essential features in mind and having a comprehensive understanding of the classification given above, we are in a position to discuss the diagnosis and therapy of individual abdominal diseases. The present discussion will be limited to culling out of the various procedures those means for arriving at a diagnosis of peptic ulcer which elicit data capable of definite interpretation, so that we may be able to say honestly that we can or cannot make a diagnosis in a given case; that is, the diagnosis and treatment of peptic ulcer, based upon clinical experience and experimental observations on patients, will be discussed.

The means for obtaining data for the diagnosis of peptic ulcer—*i. e.*, ulcer of stomach or duodenum—are, in the order of their importance:

1. History and general physical examination.
2. *x*-Ray studies of the gastro-intestinal tract.
3. And of least importance, but never to be neglected, a certain few simple laboratory procedures.

The general physical examination is important not because of its direct application to the diagnosis of ulcer, but because it affords a means of detecting other conditions which give rise to abdominal pain; such as tabes, pleurisy, lead-poisoning, etc.

History is the all-important feature in the diagnosis of peptic ulcer. Not infrequently the history affords the only evidence on which the diagnosis can be based, and it is practically always the

deciding factor in the diagnosis. The history of peptic ulcer divides the symptomatology of that disease into two forms—the typical and the atypical. The history of the typical form of peptic ulcer is rarely simulated by any other condition. The most characteristic feature of the typical form of ulcer is the time relation of the pain to meals. The pain occurs at a definite time after meals. The pain may occur just after eating or at any other time thereafter; but whatever the interval is, the pain always recurs at that particular time. The pain may occur after all three meals or after two or any one of them, depending upon the size of the meal, the character of the food, the activity of the ulcer, etc. The description of the pain itself is of little moment; it may be of any character and vary from mild to excruciating severity. It may disturb sleep, usually in the early morning hours. The feature next in importance to pain in the diagnosis of ulcer is the periodicity of the symptoms. This merely means that the symptoms remit and then relapse, remit and again relapse, and so on. The following case report illustrates the findings in the typical form of peptic ulcer.

Case I.—White male, car starter, aged forty-seven.

Diagnosis: Duodenal ulcer.

The patient complained of epigastric pain. The past medical history was essentially negative.

Gastro-intestinal History.—The onset of gastric symptoms occurred six years prior to consultation. It was characterized by distress and sharp pain in the epigastrium, occurring regularly from one hour to one and one-half hours after meals. The pain radiated to the dorsolumbar region. The pain persisted for from one to two hours unless relieved by the ingestion of soda or food. Pain did not disturb the patient's sleep. Since the onset attacks similar to the one described had occurred at intervals of about every three months and persisted for two weeks at a time. There had been no vimiting, no jaundice, and no bloody or tarry stools.

Physical examination, including that of the abdomen, was essentially negative.

Roentgen Report.—The stomach was normal in position and contour. It was slightly atonic and contained practically the

entire six-hour barium residue. Peristalsis was vigorous and the waves deep. The sphincter was normal. The duodenal cap could not be completely filled and its lesser curvature side was constantly irregular. There was only a trace of the barium in the small intestine at the six-hour observation.

Interpretation.—The findings are those of duodenal ulcer.

Clinical Pathology.—The fasting gastric contents contained no food residue. Free HCl was 50. The benzidin test for occult blood was negative. After an Ewald test-breakfast free HCl was 85 and total acidity 100. Wassermann reaction in the blood-serum was negative. The usual examinations of the blood and urine were negative.

The distinguishing feature in the history of this case is the constancy of the time relation between the taking of food and the onset of epigastric pain, as was pointed out in discussing the symptomatology of the history given in the typical form of ulcer. The above case history brings out two other features of some diagnostic importance—*i. e.*, the recurrence of remissions and exacerbations and the relief of pain by soda or food. Pain occurring at night, very often during the early morning hours, was not present in the above case; but it is a disturbing feature in many cases.

Hematemesis, or the passage of bloody or tarry stools, is of great diagnostic importance. These phenomena occur in about 20 per cent. of the cases[1] some time during the course of the disease. But since the disease lasts for years, the occurrence of hemorrhage is not very common during any one exacerbation of the activity of the ulcer.

Although the history described for the typical form usually permits a correct diagnosis to be made, occasionally such a history is obtained, while at operation no evidences of gastric or duodenal pathology are obtained. The following case report is used as an illustration of such a condition:

Case II.—White male, laundry foreman, aged thirty-nine years.

[1] McClure, C. W., and Reynolds, L.: Boston Med. and Surg. Jour., 1920, clxxxiii, 321.

Diagnosis.—Preoperative diagnosis, duodenal ulcer; postoperative diagnosis, question of chronic appendicitis as cause of symptoms.

The patient complained of epigastric pain. The past medical history was essentially negative.

Gastric History.—The onset occurred seven years ago. It was characterized by fairly severe epigastric pain occurring one hour after meals and relieved by induced vomiting. This attack lasted three weeks. During the past seven years attacks, similar to the one described, had occurred periodically. The present attack began five days prior to consultation. The pain was relieved by vomiting or by alkalis. There had been no hematemesis, no bloody or tarry stools, and no jaundice.

Physical examination was essentially negative.

Roentgen Report.—The stomach was normal in position and tone, and its outlines were regular. The antrum and pyloric sphincter were normal. Peristalsis was of the exaggerated type. The stomach emptied itself completely in one hour's time, and in six hours the head of the barium column had reached the descending colon. The first portion of the duodenum filled completely and was regular in outline.

Interpretation.—Hyperperistalsis and marked hypermotility, very suggestive of duodenal ulcer.

Clinical Pathology.—After an Ewald test-breakfast free HCl was 30 and total acidity 60. No occult blood was demonstrated by the benzidin test. The Wassermann reaction in the blood-serum was negative. The usual clinical examinations of the blood and urine were negative.

At operation no lesions were demonstrable in either the stomach, duodenum, or gall-bladder. A chronically diseased appendix was removed.

Following the operation the patient has been free from symptoms for six months and has gained much weight.

Given the history of the characteristic type of pain described, and especially if periodicity also is present, the diagnosis of peptic ulcer will usually be correct. But in view of the case just cited (Case II) one is hardly justified in resting the diagnosis on

the history of the neglect of a means which will permit of objective examination of the stomach or duodenum. This is afforded by *x*-ray. Fluoroscopic examination and, if necessary, *x*-ray plates should be made in all cases, because the findings are usually highly indicative of ulcer, and occasionally they are diagnostic. The clear-cut history, which is given by the majority of ulcer patients, together with the usual *x*-ray findings, enables the diagnosis of the typical form of peptic ulcer to be made with a high degree of accuracy.

The *x*-ray findings in ulcer are of two general types; that due to muscular abnormalities, such as spasm, and that due to penetration of the gastric wall by the ulcer. The latter produces the well-known lesion called the niche, which is diagnostic of peptic ulcer. Unfortunately, it is not the usual finding, and the evidence of ulcer is given by localized muscle spasm only. Localized muscle spasm in the stomach or duodenum occasionally occurs as the result of conditions outside the alimentary canal. It is, therefore, merely a physical finding and is not in itself diagnostic of ulcer,[1] as is illustrated by the following case report:

Case III.—White male, salesman, aged thirty-two years.

Diagnosis.—Gastric neurosis.

Patient complained of epigastric burning. The family and past medical histories were unimportant.

Gastric History.—From February to November, 1914 the patient had had attacks of slight dizziness with some nausea and occasionally vomiting, but no hematemesis or bloody or tarry stools. The attacks recurred after two or three weeks and lasted about half a day. In November, 1914 severe epigastric burning from two to three hours after meals began; this symptom persisted for two weeks. The patient was then placed on a diet, which was followed for several months, with finally complete relief from symptoms. The patient remained well until the present illness, October, 1919. About the first of that month the onset of mild burning in the epigastrium, from two to three

[1] See also McClure, C. W., and Reynolds, L.: Interpretation of Roentgen-ray Findings in the Diagnosis of Peptic Ulcer, Jour. Amer. Med. Assoc., 1920, lxxiv, 711.

hours after meals, began. The symptoms gradually increased in severity, until at the end of three weeks the patient sought medical advice. The appetite was good. There had been no vomiting. The bowels were constipated. There had been no loss in weight.

Physical examination was essentially negative.

Roentgen Report.—The stomach was normal in position and tone. Its outlines were regular. There was active peristalsis and the pyloric sphincter closed normally. There was constantly present a definite irregularity of the lesser curvature side of the first portion of the duodenum. Otherwise the duodenum appeared normal.

Interpretation.—The findings are those usual in ulcer of the first portion of the duodenum.

Roentgen-ray studies were repeated in two days and again one month later. On both occasions the duodenum filled normally and its outline was regular.

Clinical Pathology.—Gastric analysis was not made. The stools gave a negative benzidin test for blood. The usual examinations of the urine and blood were negative. The Wassermann reaction in the blood-serum was negative.

Subsequent study of this case made the diagnosis of a neurosis seem to be certainly correct.

Hypermotility is an *x*-ray finding very characteristic of certain types of duodenal ulcer. Not infrequently in the presence of a duodenal ulcer the stomach will empty itself of the ordinary barium *x*-ray meal within one hour's time, while under normal conditions the stomach empties itself in from three to six hours. However, hypermotility is not diagnostic of duodenal ulcer, as is shown by the findings in Case II.

There is a group of peptic ulcer cases whose symptomatology is atypical and not infrequently simulates more or less closely that of other abdominal conditions. There is the type of ulcer with pain like that commonly found in cholelithiasis; the site of the pain may be in the gall-bladder region, but more frequently it is located in the epigastrium. The history of periodic recurrences

of this type of pain is often obtained and is very helpful in making the diagnosis of ulcer.

Case IV.—White male, tailor, aged fifty-two.

Diagnosis.—Preoperative diagnosis, chronic cholecystitis; postoperative diagnosis, gastric ulcer.

The patient complained of abdominal pain. The past medical history is unimportant.

During the past fifteen years there had been attacks of severe pain, beginning in the gall-bladder region, radiating around the right costal margin to the back and up under the right scapula. The point of maximum intensity was in the right axillary line just above the costal margin. The onset of pain was abrupt, and the latter persisted from fifteen to thirty minutes. Pain occurred at any time of the day or night and bore no relation to meals. From two to ten painful attacks occurred a day, and were accompanied by much belching. The attacks persisted for a couple of weeks, then disappeared, not to recur for a year to two. The patient had never vomited, although he had often been nauseated. There had been no jaundice, dark urine, or clay-colored, bloody, or tarry stools.

Physical Examination.—The physical examination was essentially negative.

Roentgen Report.—Esophagus was normal in outline. The postion of the stomach was slightly to the left of the midline. There were rather shallow peristaltic waves. There were no tender points on palpation over the stomach. It was freely movable and no filling defects were seen. Its outline was regular, but there was a marked prepyloric bulge. Duodenum was small, the cap could not be filled. It was drawn well up under the gall-bladder region, was in an oblique position, but was not tender on palpation. Ileum was low, freely movable, and showed a small shix-hour residue. The head of the column of barium was in the cecum at the end of six hours; at the end of twenty-four hours it was in the sigmoid. Cecum filled normally, was freely movable, and showed no tender points. It contained a twenty-four-hour residue. Appendix was not visualized. Colon filled normally, had a rather low position, and no fixed acreas were discovered.

Interpretation.—Incomplete filling of first portion of duodenum is suggestive of ulcer.

Clinical Pathology.—The fasting stomach contents contained free HCl 15 and total acidity 38. The benzidin test was negative. Gastric contents after an Ewald test-breakfast contained free HCl 58 and total acidity 70. Two stools contained no occult blood. The usual examinations of blood and urine were negative. The Wassermann reaction in the blood-serum was negative.

Surgical Note.—The patient was operated upon for supposed gall-bladder disease. The gall-bladder was opened and showed nothing pathologic. The first portion of the duodenum was tied to the gall-bladder by a broad, vascular, congenital band of connective tissue. This band arose from the proximal two-thirds of the gall-bladder, crossed the duodenum, and was inserted in the transverse mesocolon. An old ulcer was found in the inferior surface of the pyloric sphincter and had constricted the entire pyloric ring.

There is a type of ulcer characterized by vomiting. Very often the vomiting attacks occur periodically and the periodicity is helpful in making the diagnosis. The following case report illustrates such a case:

Case V.—White male, attorney, aged sixty years.

Diagnosis.—Chronic duodenal ulcer.

The patient complained of vomiting. Family and past medical histories were negative.

Gastric History.—For the past forty years the patient had had periodic attacks of vomiting occurring a few times a year and persisting for weeks. During an attack ten years ago a severe hematemesis occurred. Medical treatment for gastric ulcer was taken with apparent recovery. Since then until the summer of 1918 the patient had remained free from symptoms. In July, 1918 an attack similar to the present one occurred. *x*-Ray studies at that time showed a deformity of the first portion of the duodenum. Medical treatment for duodenal ulcer resulted in complete arrest of symptoms, except for some occasional epigastric distress quickly relieved by soda, until the onset of the present illness. The latter began two weeks before the patient

came under observation. During this period there had been some belching, and on one day vomiting (no hematemesis) preceded by slight epigastric distress. The vomitus had contained lettuce, ingested twelve hours previously. During the thirty-six hours prior to observation the patient had vomited frequently. This vomitus consisted of considerable quantities of greenish, non-bloody, non-food-containing liquid. No pain or epigrastric distress had been present.

The physical examination was negative except for the abdomen. Just to the right of the umbilicus was an easily palpable, small, sausage-shaped, hard, and freely movable tumor. Two days later, after the cessation of vomiting, the abdominal tumor had disappeared, although the character of the abdomen was favorable for palpation.

Roentgen Report.—The stomach was normal in position and tone and its outlines were regular. The antrum and pyloric sphincter were normal. Peristalsis was active, at times vigorous, nevertheless there was a moderate-sized six-hour barium residue. The first portion of the duodenum was oblique in position. The outline was constantly irregular on the lesser curvature side of this portion of the duodenum.

Interpretation.—The findings are those of an ulcer in the first portion of the duodenum.

Clinical Pathology.—Examination of the different specimens of vomitus showed no food residues, even when solid food had been taken twelve hours previously. Free HCl was present. The benzidin test for blood was negative. The stools contained no occult blood. The Wassermann reaction in the blood-serum was negative. The usual examinations of the blood were negative. The urine contained a few red blood-cells due to a mild grade of chronic prostatic disease.

In addition to the two atypical forms of peptic ulcer described there is a form in which, as a result of hemorrhage and malnutrition, either due to limited food intake or pyloric obstruction, the symptom-complex simulates that of cancer. Under these circumstances the *x*-ray will usually allow the correct diagnosis to be made. Occasionally marked hemorrhage or more rarely

perforation is the first symptom which leads the patient to seek medical advice.

In making the diagnosis of the atypical types of peptic ulcer x-ray studies are invaluable. If a penetrating lesion, or niche, is found, the diagnosis is assured; if localized muscle spasm is found, the correctness of the diagnosis of ulcer is highly probable. Should the x-ray findings be negative, as occasionally happens, careful medical treatment for ulcer may be given. If, however, in the type simulating gall-stone colic, severe pain continues in spite of medical treatment, operative measures may be considered. On the other hand, vomiting is caused by such a variety of conditions that if it is the only symptom present operation would hardly be advisable in the absence of pretty positive x-ray findings of ulcer. If vomiting in a patient is due to peptic ulcer, it will be relieved by proper medical treatment and sooner or later symptoms more characteristic of ulcer will develop.

So far nothing has been said about the laboratory findings. The most important of these is gross inspection of the vomitus for visible blood and for food retention, and of the stools for gross amounts of blood. These findings must be interpreted in relation to the history given by the patient and the other findings in the case, for they may arise from causes other than benign ulceration. Of the other laboratory findings, the presence of free HCl in the gastric contents has some importance in differentiating between peptic ulcer and cancer, while the presence of occult blood on repeated examinations has but slight diagnostic value. On the other hand, the persistent presence of occult blood in the stools indicates hemorrhage in the gastro-intestinal tract.

In taking up the question of treatment of peptic ulcer it is emphasized that all available methods, either surgical or medical, are but makeshifts, for we have no direct means of bringing about a cure. As is usually the case when a diseased process must be combated by indirect means, there is considerable diversity of opinion regarding the best method or methods of the therapy of ulcer. Nevertheless, by the use of any of the recognized medical or surgical methods, either alone or combined, the majority of ulcer patients can be very largely relieved of unpleasant symp-

toms. Regarding the question as to operation versus medical treatment I feel that all of us had better maintain an open mind; for I do not believe that, except in certain conditions, such as organic pyloric obstruction, it is definitely established which plan of therapy gives the best results. However, there are a considerable number of patients who desire to take the medical treatment of ulcer and who remain in good health by adhering to certain dietary principles. There are, furthermore, various economic factors which favor medical treatment. The latter is much less expensive than surgical therapy; also, often the patient can be treated at home. A certain number of ulcer patients can do a part, at least, of their work while under medical treatment. There is no reason why the general practitioner of medicine should not treat the average case of peptic ulcer, which is another saving for the patient. But whether or not medical treatment or surgical operation is to be advised in the average case of peptic ulcer is very properly governed at present by the personal opinion of the physician in charge of the patient.

However, there are certain indications for surgical treatment on which agreement is general. A brief and very good discussion of these indications is given on page 150 of Vol. III in Oxford Medicine, and they are outlined as follows:

1. When there is reason to suspect carcinoma.
2. Perforation into the free peritoneal cavity.
3. Organic pyloric obstruction of such degree as to materially affect the emptying of the stomach.
4. Hour-glass stomach due to organic constriction.
5. Hemorrhages recurring in spite of proper medical treatment.
6. Perigastric abscess.

Knowledge of the physiology and pathologic physiology of the stomach and duodenum aid in understanding the rationale of medical treatment. I must ask that you forget the great majority of what you have been taught and have read concerning the physiology of the alimentary canal in man; for what you have learned is usually not what has been observed to occur in man, but what occurs in the lower animals. Whether the phe-

nomena which occur in these animals also occur in man is an open question; and Dr. Reynolds, Mr. Wetmore, and the author have made experimental observations which lead us to believe that there are vitally important differences in the gastro-intestinal tract of man and the lower animals. For this reason a discussion of certain phases of the physiology and their relation to the pathology of digestion in men will be given. These observations are the result of our own work, some of which has been published.[1]

Just as soon as food is ingested by a normal man peristaltic waves run along the stomach to the pyloric sphincter at regular intervals. As each wave approaches the sphincter the latter opens and allows food to pass from the stomach into the duodenum; that is, provided the food eaten has been finely divided, such as ground meat, or is in the form of liquids. Finely divided food is not retained in the stomach and churned up in the manner described in the text-books of physiology. The mass of the food apparently leaves the stomach of normal man largely undigested, which is, again, contrary to the usually accepted idea. Each time a peristaltic wave pushes a bolus of food through the sphincter that food is ejected into a relatively large amount of liquid present in the duodenum. For example, we estimate that each ½ pint of cream, ingested by a normal man, is mixed with from 5 to 10 quarts of fluid in the duodenum. Our observations indicate that the kind of food eaten (that is, carbohydrate, protein, or fat) governs the amount of liquid poured into the duodenum. Carbohydrates bring forth the least amount of liquid and fats the most. The offices of this liquid are two: (1) to neutralize the acidity of the food coming into the duodenum from the stomach, and (2) evidently to furnish the proper conditions for the digestion of food in the intestines, where the majority of it is digested.

[1] On the Behavior of the Pyloric Sphincter in Normal Man, McClure, C. W., Reynolds, L., and Schwartz, C. O., Arch. Int. Med., 1920, xxvi, 410 Physical Characters and Enzymatic Activities of Duodenal Contents, McClure, C. W., Wetmore, A. S., and Reynolds, L., Jour. Amer. Med. Assoc., 1921, lxxvii, 1468. Motor Phenomena Occurring in Normal Stomachs, in the Presence of Peptic Ulcer and its Pain, as Observed Fluoroscopically, Reynolds, L., and McClure, C. W., Arch. Int. Med., 1922, xxix, 1.

The normal stomach empties itself of an average sized meal in about six hours, although a small residue may remain several hours longer. Our observations show that a residue of one meal is in the stomach when it is time to take a second meal; that is, lunch is taken on top of a gastric residue from breakfast, and dinner, on one remaining from lunch. Hence, the digestive apparatus of normal man is at work the greater part of each twenty-four-hour day. Our observations show further that when food which has not been thoroughly masticated, that is, finely ground up, is ingested, it remains in the stomach until it has been disintegrated; and it seems that disintegration of food masses is one of the important functions of the stomach. It is obvious, therefore, that the more finely divided the food which enters the stomach, the less the work is which the stomach has to do. The significance of these findings in their relation to the medical treatment of ulcer will be discussed later.

In the presence of an active ulcer, either gastric or duodenal, the motor functions of the stomach show various well-marked deviations from the normal. Rather rarely in duodenal ulcer the pyloric sphincter acts as though it were in a state of relative relaxation, while gastric peristalsis is regular and vigorous. Under these conditions the stomach may empty itself in one or two hours instead of taking the normal time of about six hours. Not infrequently, however, at the end of six hours the stomach, in the presence of a peptic ulcer, has not emptied itself, and a considerable food residue will be found in it. So far we have observed but one cause for this retention of food, and that is intermittent pylorospasm. When this is present the pyloric sphincter does not open as each peristaltic wave approaches, as happens in the normal stomach, but it only opens at irregular intervals, in spite of the fact that gastric peristalsis is regular and vigorous. As a consequence of this intermittent opening of the sphincter the emptying time of the stomach may be delayed. We have watched some such stomachs over periods of ten hours, during which time the stomach would not empty itself of more than one-half of the original meal. However, intermittent py-

lorospasm is not always accompanied by delay in the emptying time of the stomach.

There is another type of gastric peristalsis brought about in some way by the presence of peptic ulcer. This type is characterized by irregularity in the times of occurrence, the size and the depth of the peristaltic waves. Many of these waves are so weak as to be able to force little or no food through the sphincter into the duodeum. In the presence of this type of peristalsis it was often observed that but little food left the stomach at first, but after one-half to two hours the stomach emptied itself rapidly.

During the paroxysms of pain of peptic ulcer the motor activity of the stomach shows usually one of two types of abnormality. In one there is marked pylorospasm with vigorous, regular peristaltic waves in the stomach; in the other complete or almost complete cessation of gastric peristalsis develops. In certain instances other motor evidences of spasm of the gastric musculature are also found, but these are of minor significance and will not be discussed.

That the abnormal motor phenomena described are the cause of pain and other gastric symptoms occurring in peptic ulcer is questionable. But they do afford objective means for controlling the effects of any plan of treatment; for it has been found that changing the abnormal motor and muscular phenomena back to the normal is accompanied by relief of symptoms. For instance, our observations have shown that the ingestion of alkali or of food often changes an abnormal type of motor activity back to the normal type, and accompanying this change pain disappears. We have also observed that when an ulcer becomes clinically cured, *i. e.*, quiescent, the abnormal motor phenomena described disappear.

Knowledge of the normal and abnormal phenomena which have been outlined above are very useful in deciding the principles upon which the dietary measures to be used in the treatment of active peptic ulcer are to be based. These principles are as follows:

1. The giving of liquids and foods which can be easily finely divided.

As has been discussed, the emptying of the stomach is either delayed or abnormally rapid in the presence of peptic ulcer. If the emptying time is delayed, it seems wise to give foods of a character which are known to leave the normal stomach readily. Such foods are those which are liquid and those that can be easily disintegrated. If the emptying time of the stomach is abnormally rapid, it seems wise to give the same kinds of foods on the basis that their physical character will enhance intestinal digestion.

2. The giving of foods at frequent intervals.

Our observations show that abnormal motor phenomena of the stomach may be changed and unpleasant symptoms ameliorated by the taking of food. For this reason it has been deemed wise to give food at frequent intervals, and because of the frequency, in small amounts. It may be pointed out here that the constant presence of food in the stomach, due to the frequency of the feedings, entails no more work on the part of the digestive apparatus than occurs under normal conditions of eating, as has already been discussed.

3. The giving of alkalis.

Alkalis have been found to produce a marked effect on abnormal motor phenomena of the stomach; which effect is accompanied by the disappearance of pain.

4. The food should be of such quality and quantity as to maintain the patient in a normal state of nutrition and health.

5. The dietary measures must be of such a nature that they can be easily adhered to by the patient.

It has further been considered best to limit the intake of those types of foods which cause the pouring of the largest amounts of liquid in the duodenum, because we have made a number of observations which indicate that this lessens the motor activity of that region—*i. e.*, allows a relative state of rest. For this reason the use of fats has been restricted in the diets we have employed.

The principal ingredient of the diet we usually employ in the treatment of active peptic ulcer is milk. This is because milk is easily obtained, convenient to carry, requires no preparation

before being taken, and the amounts taken can be readily varied. For these reasons it can be taken at frequent intervals by the laborer at his work or the broker in his office. If the patient is ill enough, milk is the only food given for a few days to a week, but ordinarily other foods can be given from the outset of the treatment. Using milk as a basis, other foods can be added at the discretion of the physician.

In the majority of cases the diet is as follows:

Breakfast: Poached egg, toast. Cereal, as Cream of Wheat or Farina, cream, and sugar.

Noon: Soups (not containing coarse vegetables and not made from meats), crackers, bread, toast, butter, custards, jellies, cooked egg is desired.

Night: Same diet as at noon.

From 7 A. M. to 8 P. M. $\frac{1}{2}$ to $\frac{3}{4}$ glass of milk every hour. Every two hours the patient is given an alkali. For the sake of the patient's convenience he is usually given a box of powder containing a mixture of 100 gm. $NaHCO_3$, 30 gm. $CaCO_3$, and 10 gm. aromatic powder, of which a teaspoonful is taken. If the patient's pain is not controlled by the two-hourly dose, the powder is given every hour. The majority of ulcer patients are constipated, and for this reason they are given an alkaline cathartic powder, as follows: sodium bicarbonate 100 gm., magnesium oxid 60 gm., and aromatic powder 10 gm. Of this as many teaspoonfuls are taken each day as are necessary to produce bowel movement.

The patient is kept on this régime until all symptoms have disappeared, and for one to two weeks thereafter; usually a total of three to six weeks. During this time the majority of patients gain a number of pounds in weight. The diet is now gradually varied, each new food being added in small amounts to test the tolerance for it. The new foods are the tender meats, such as chicken, lamb, veal; baked or mashed potato, cauliflower, carrots and other vegetables which have been seived; the pulp of cooked fruits. A week or two after all symptoms have disappeared the feedings may be divided into the three regular meals a day, supplemented by milk and crackers in the middle of the morning and

afternoon. The patient is informed that the principles of the dietary measures are: (1) to divide the daily food intake into five portions fairly equal in amount, and (2) all foods swallowed must be tender and thoroughly ground up, all vegetables are to be served as purées (that is, seived to make them fine).

At this time a remark on the use of salt in the diet will be made. Dr. Nelson M. Wood,[1] in a study of 100 peptic ulcer patients, found that many of the patients progressed more favorably after limiting the amount of salt added to their food. Depending upon the individual case the limitation of salt varied from a salt-free diet to one in which no salt was added after the food had been prepared for the table. Certainly this simple procedure is worthy of trial in those cases which are not progressing satisfactorily.

Success in dietary treatment of peptic ulcer depends as much on the intelligent co-operation of the patient as it does in diabetes or nephritis. Ulcer patients should be kept under observation until they thoroughly understand the principles of treatment and until they have learned how to apply those principles to their own case.

It may be urged that the frequency of the feedings makes the regimen impractical. But such an objection is theoretic, since the author has many laborers, clerks, and other working persons who have taken the treatment for acute ulcer and are now taking the five meals a day and experience no inconvenience from the diet.

Rest, as in most other medical conditions, is an essential feature of the treatment of peptic ulcer. It is advisable for the patient to be at complete rest until he has become free from symptoms; and then to be gotten up gradually. On the other hand, it frequently occurs that the less well-to-do patient cannot rest except as an emergency, for economic reasons. Ambulatory treatment may be tried under such circumstances. In this event the amount of work which the patient can do without causing severe pain is determined, and which will, also, permit amelioration of the symptoms within four to five weeks at the most.

[1] Personal communication.

When gross hemorrhage occurs the patient should be put to bed at complete rest and quieted by morphin. Nothing is given by mouth except the alkali powders, every hour, for two or three days. During this time thirst is allayed by cracked ice. Then feedings of an ounce of milk every hour are commenced on the second or third day, and increased a little each day, until at the end of a week the usual amount is being taken.

Other factors of more or less importance in the treatment of peptic ulcer are those of general physical and psychologic hygiene. Foci of infection should be gotten rid of when they exist. The patient should attempt to free himself from unnecessary worries and responsibilities. It is not to be forgotten that there are a certain number of peptic ulcer patients who enjoy good health unless they are subjected to an undue amount of emotional strain.

The disappearance of the symptoms, after the return to a fairly general diet, has afforded almost the only available means for judging the progress of a patient under treatment for peptic ulcer. But the recent work of Reynolds and the author has added an objective means which aids in forming a better opinion as to the patient's progress. This means consists in feeding the patient a meal composed of 200 gm. ground, lean beef baked into a loaf with 40 to 90 gm. barium sulphate, and ground up with 200 c.c. of water, and observing the phenomena occurring in the stomach and pyloric sphincter through the fluoroscope. The normal and abnormal phenomena which may occur have already been described.[1] By the use of this method a certain number of patients have been observed in whose stomachs abnormalities could be demonstrated fluoroscopically at a time when the patients were apparently clinically "cured." Such findings indicate that the ulcer is still active and necessitate further careful observation and treatment of the patient.

[1] Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomachs in the Presence of Peptic Ulcer and its Pain, as Observed Fluoroscopically, Arch. Int. Med., 1922, xxix, 1.

CLINIC OF DR. EDWIN T. WYMAN

BOSTON FLOATING HOSPITAL

DIARRHEA: FERMENTAL AND INFECTIOUS

I WISH to present to you and discuss the treatment of 2 cases, one of fermentative diarrhea with alimentary intoxication, the other of infectious diarrhea.

CASE I

H. C., a male, aged three months. His family history was negative. He was a full-term baby and was born after a normal labor. His birth weight was unknown. He was breast fed for seven weeks and gained steadily. The mother's milk then failed and he was put on a formula containing whole milk, 4 ounces; boiled water, 4 ounces; cane-sugar, 1 teaspoonful.

The percentages would be 2 per cent. fat, 2¼ per cent. lactose, 4¾ per cent. sucrose, 1.60 per cent. protein. He was fed 3½ ounces every three hours and two or three times during the night. One week ago oatmeal-water was used in place of the boiled water. Four days ago the baby started to have a diarrhea. He had green, watery movements, five to seven daily. The formula was then changed to a mixture consisting of whole milk, 8 ounces; boiled water, 8 ounces; Mellin's Food, 3 level tablespoonfuls.

The percentages of this mixture would be 2 per cent. fat, 7 per cent. carbohydrate, of which 4.75 per cent. was in the form of Mellin's Food, 1.60 per cent. protein. The diarrhea increased and the baby had a good deal of gas and seemed to suffer from colic. The stools continued to be loose and he had from eight to ten daily. He vomited practically every feeding taken during the next twenty-four hours. He looked very sick when brought to the Boston Floating Hospital soon after.

Physical Examination.—On admission to the hospital he was fairly well developed and poorly nourished, but of fair color. He looked very toxic and his tissues were considerably dehydrated. The skin was smooth, soft, dry, loose, and easily picked up. He was fretful and cried feebly. His features were

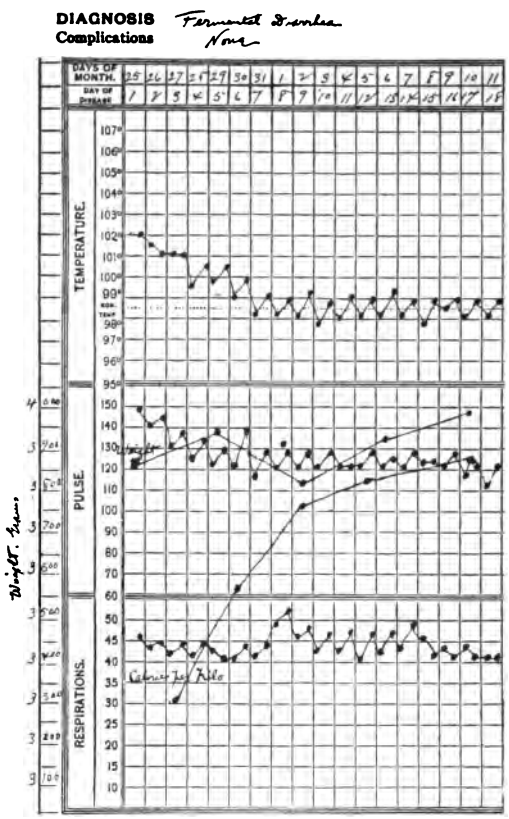


Fig. 267.—Case I.

pinched and the eyes glassy, the cornea being covered with a film. The fontanel was a little depressed. There was no rigidity of the neck or neck sign. The pupils were equal and reacted to light. The mouth was dry and the tongue slightly coated. The heart and lungs were normal. The abdomen was flat. There was no localized muscular spasm. The liver was pal-

pable 2 cm. below the costal margin. The spleen was not palpable. There was considerable spasm of both arms and legs, with a tendency to twitching. There was no paralysis. The knee-jerks were equal and lively. Kernig's sign was absent. There was no enlargement of the peripheral lymph-nodes. His weight on admission to the hospital was 3856 grams. The rectal temperature was 102° F. The urine was pale, acid, and contained neither albumin nor sugar. There was a slight acetone reaction and the sediment showed many urates, but no casts, blood, or pus. The von Pirquet test was negative. The hemoglobin was 50 per cent. (Sahli). The white blood-count was 12,600. The stools were watery, dark green in color, and had an acid reaction. They showed considerable mucus, but no blood or pus. The agglutination test for Bacillus dysenteriæ was negative.

Diagnosis.—A diagnosis of fermentative diarrhea with alimentary intoxication was made. The green, foul movements, the high temperature and evidence of toxic absorption show that there is something more than a disturbance of the equilibrium of digestion, that fermentative processes are going on in the bowel, and that the condition is, to some extent, bacterial in origin.

The term "fermentative" is used not in the limited sense in which it is sometimes used to describe carbohydrate fermentation alone, but in its broad sense, to describe all the results of bacterial growth and activity. In almost no aspect of scientific medicine is our knowledge so deficient as in intestinal bacteriology. The subject is so enormously complicated and its investigation attended by such technical difficulty that at the present day we cannot say that more than a beginning has been made in its study. Carbohydrate fermentation may be in excess and produce the symptoms. On the other hand, protein putrefaction may be in excess, either through the introduction, from without, of obligate putrefiers or from the organisms attacking the protein. The actual existing causes which lead to excessive abnormal bacterial fermentation in the intestines are not clearly understood. Possibly a number of factors are concerned, some

operating in one case, others in another. The absence of blood and pus in the stool, together with the negative serum reaction, would rule out infectious diarrhea. Meningitis was ruled out by the depressed fontanel and by the fact that meningitis is a very unusual complication of acute diarrheal diseases of infancy, while symptoms of meningeal irritation are not at all uncommon. The nervous symptoms were merely evidences of toxic absorption and possibly in part due to the high temperature.

Treatment.—The baby was given 2 teaspoonfuls of castor oil on admission to the hospital, as it was felt that it was best to thoroughly clean out the bowel before beginning treatment, and the baby seemed sufficiently strong to stand the catharsis. After six hours, during which time the baby was given boiled water with saccharin 1 grain to the quart, he was started on a mixture of fat-free lactic acid milk one-quarter and boiled water three-quarters. This mixture contained the following percentages: 0 fat, 1.40 per cent. carbohydrate, 0.80 per cent. protein. This was given in small amounts every three hours and as much water as possible was given between these feedings. The baby vomited considerably the first day, but the next day the vomiting was less severe. He was given normal saline solution intraperitoneally, one infusion each day, of 190 c.c. each for the first two days. The general condition improved and he seemed much less toxic. On the third day the formula was increased to one-half fat-free lactic acid milk and one-half barley-water, with dextrimaltose No. 1 added up to 5 per cent. He still continued to be very toxic and took his food very poorly. He gradually improved, however, and on the seventh day the formula was increased to 16 per cent. cream, 2 ounces; fat-free lactic acid milk, 14 ounces; 1½ per cent. barley-water, 16 ounces; dextrimaltose No. 1, 3 level tablespoonfuls.

The percentages of this mixture were 1 per cent. fat, 2.25 per cent. lactose, 3.75 per cent. dextrimaltose, 1.60 per cent. protein, 0.75 barley starch. He retained this formula and the stools became less frequent and more normal in character. The fat was then increased to 1.25 per cent. on the ninth day, and on the thirteenth day the formula was changed to a whole

milk mixture consisting of whole milk, 14 ounces; 1½ per cent. barley-water, 16 ounces; boiled water, 2 ounces; dextrimaltose No. 1, 3 level tablespoonfuls.

This formula contains 1.50 per cent. fat, 6 per cent. dextrimaltose, 1.20 per cent. protein, 0.75 per cent. barley starch. He took his food very well and was having three to four stools daily. They were yellow, soft, alkaline, and contained no mucus. He was discharged well on the eighteenth day after admission. His weight on admission to the hospital was 3856 grams. He lost 3714 grams on the ninth day after admission, and after that time gained steadily, until on the day of his discharge from the hospital he weighed 3997 grams.

In severe toxic cases in which the tissues are dehydrated it is often inadvisable to give the initial dose of castor oil, as the baby is in a too weakened condition to stand the catharsis. If the vomiting persists and the intoxication increases when small amounts of food are given, and the symptom-complex is strongly suggestive of a relative acidosis, it is better to withdraw the food for twenty-four hours and give intravenous injections of 10 per cent. glucose solution, 10 c.c. per pound of body weight. This should be given once or twice in the twenty-four hours. The longitudinal sinus should be used only in the extreme cases where it is impossible to use a vein. Intrasinus injections are always, even under ideal conditions, accompanied by some degree of danger either from hemorrhage or thrombosis. Intraperitoneal infusions of normal saline solution can be given once or twice in twenty-four hours, the amount depending upon the individual. Usually from 90 to 300 c.c. may be given.

In cases of severe prostration and collapse the best stimulant is fluid given intravenously into the longitudinal sinus. Other stimulants which may be used in collapse are adrenalin, caffein, or sodium bromid. The adrenalin should be given in doses of $\frac{1}{8}$ to $\frac{1}{2}$ grain, subcutaneously. For toxic nervous symptoms, such as restlessness, sodium bromid is the best drug, given by mouth in doses of 5 grains. If the anterior fontanel is bulging, lumbar puncture will often give relief. Ice-bag to the head should not be used unless there is high fever, and then

must be used cautiously. For excessive vomiting the stomach should be washed out with a solution of sodium bicarbonate, 1 teaspoonful to a pint of water. This may be repeated daily. Little else can be done.

When food is begun I believe that fat-free lactic acid or Eiweiss milk are the best routine treatment for these cases. The amount of dilution depends, of course, upon the individual. Eiweiss milk should be used when it is desired to get a lower sugar than is possible with lactic acid milk. The object of using lactic acid milk is the inhibition of abnormal bacterial activity and the restoration of normal bacterial conditions in the intestinal canal. The abnormal bacteria cannot be completely removed by purgatives and will continue to ferment all food given unless combated in some other way. Intestinal antiseptics are absolutely useless because they cannot be given in doses large enough to destroy the bacteria without danger to the patient. The offending micro-organisms cannot be removed by irrigating the colon because they are situated mainly in the small intestine, and the fluid given in a colon irrigation does not go above the iliocecal valve.

There are two ways in which the abnormal bacterial activity which is causing the disease can be checked. One way is by introduction into the intestinal canal of micro-organisms antagonistic to the offending micro-organisms. The other is by altering the chemical composition of the food in such a way as to provide a culture-medium unsuitable for the abnormal fermentation which is present. Lactic acid milk is an ideal food for the treatment of the condition in which we can never be sure of the exact character of the abnormal bacterial processes in the intestine. If the case is one of excessive carbohydrate fermentation, by using lactic acid milk we are using a food relatively high in an easily digested protein and low in carbohydrate, which is just what is needed. If the case is one of protein putrefaction the lactic acid will antagonize the proteolytic organisms and bring about a normal bacterial balance, while the carbohydrate in the food and protein protected from attack will nourish the patient. When treatment with lactic acid milk

fails to bring about an improvement in the symptoms of fermentation, the carbohydrate in the lactic acid may not be sufficiently low to prevent fermentation, or the mixture may be too strong. If the symptoms continue, with vomiting and curdy stools, the mixture should be given more diluted. If the stools continue to be acid, green, and irritating to the buttocks, Eiweiss milk should be used. This retains the advantages of the lactic acid while permitting further reduction in the carbohydrates. As soon as the symptoms of fermentation have been removed, dextrimaltose, which is less fermentable than lactose, should be added first to 4 and then to 5 or 6 per cent. Barley starch should be added up to 0.75 per cent. Gradually the lactic acid milk can be replaced with ordinary mixtures and the feeding arranged in accordance with ordinary principles of feeding. If recurrence of the symptoms occurs, the treatment must be begun over again and return to a normal diet must be still more gradual.

CASE II

A. M., female, aged two years. She was the second child of healthy parents. She was born at full term after a normal delivery and weighed 5 pounds. She was breast fed for three months, and did well. She was then put on a whole milk mixture. This mixture was gradually increased until, at the age of ten months, she was on plain whole milk. At one year she was taking cereals, toast, broth, crackers, prunes, and potato. She had always been very well up to the onset of the present illness.

Two days ago she ate a raw pear in the forenoon. During the afternoon she had three loose movements and the following day she had six very loose, foul movements, which began to show a slight trace of blood. She was feverish and vomited twice. On the morning of admission to the Boston Floating Hospital she had had three loose movements, all of which had contained a trace of blood.

Physical Examination.—She was a well-developed and nourished, though a sick looking child. The skin was clear and dry. The pupils were equal and reacted to light. The fontanel was closed. The lips were dry and parched. The tongue was clean.

The throat was normal. The tonsils were of moderate size with no inflammation. She had 14 teeth. There were a few small cervical lymph-nodes. There was no rigidity of the neck or neck sign. The heart was of normal size and position and there were no murmurs heard. The lungs were resonant throughout and

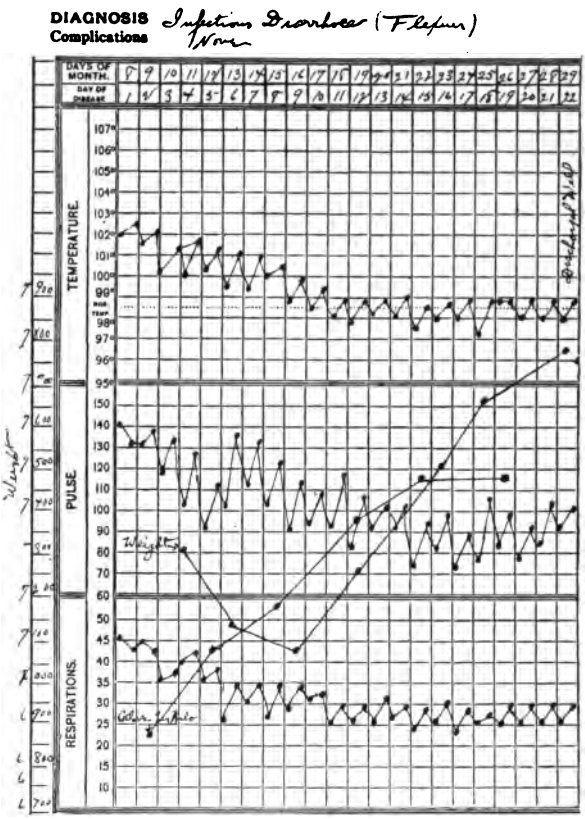


Fig. 268.—Case II.

clear. The abdomen was flat, with no distention, spasm, or tenderness. The liver was palpable 1 cm. below the costal margin. The spleen was not palpable. The knee-jerks were equal and normal. There was no Kernig, Babinski, Oppenheim, or clonus. The temperature on admission was 102° F. The hemoglobin was 65 per cent. (Sahli). The white blood-count

was 15,400. The stools were grass green, acid, and contained considerable mucus and showed the presence of both blood and pus. The test for gas bacillus was negative. The agglutination test for Bacillus dysenteriæ (Flexner type) was positive.

Diagnosis.—On admission to the hospital the fever and the stools containing blood were so characteristic of infectious diarrhea of the dysenteric type that no differential diagnosis from other forms of diarrhea was necessary. Later the agglutination test showed it to be of the Flexner type.

Treatment.—On admission to the hospital the child was given 1 tablespoonful of castor oil and an intraperitoneal infusion of 240 c.c. of salt solution. Water was forced, and she took it very well. After six hours she was started on a formula consisting of one-half Eiweiss milk and one-half boiled water. The percentages of this were 1.25 per cent. fat, 0.75 per cent. sugar, 1.50 per cent. protein. She was fed every four hours and was offered 8 ounces at a time. Between feedings water was given freely. A low sugar was given at the start, as it was thought that there was some fermentation in addition to the infection. She took the water very well, but did not like the Eiweiss milk. She vomited twice during the first twenty-four hours, but at the end of that time seemed very much improved. After forty-eight hours dextrimaltose No. 1 was added to the formula, this up to 5 per cent., and the next day the formula was increased to three-fourths Eiweiss milk, one-fourth barley-water, with dextrimaltose up to 6 per cent. On the fourth day after admission cereal and toast were added to her diet. At that time she was taking her food rather poorly, only about 400 c.c. in twenty-four hours, and 600 c.c. of water. The toast and cereal were taken very well. She seemed very much less toxic, although the temperature still remained at 100° to 101° F. The blood persisted in the stools until the fifth day, when they became more normal in character. There was mucus in the stools for some time. The diet was continued without change until the ninth day after admission. Her appetite for the milk gradually improved in this time and on the ninth day the formula was changed to one consisting of fat-free milk, 30

ounces; 3 per cent. barley-water, 10 ounces; dextrimaltose, up to 6 per cent.

Two days later 16 per cent. cream was added, bringing the fat up to 2 per cent. On the thirteenth day after admission the formula was changed to three-fourths whole milk, one-fourth 3 per cent. barley-water, with milk-sugar up to 6 per cent. The percentages of this mixture were 3 per cent. fat, 6 per cent. dextrimaltose, 2.40 per cent. protein, 0.75 per cent. barley starch. This was given, together with a normal infant diet, until her discharge on the twenty-first day after admission to the hospital.

Her weight on admission was 7300 grams. She lost 7080 grams on the ninth day. During the remainder of her stay at the hospital she gained steadily, and on the day of her discharge she weighed 7780 grams.

The symptoms in severe cases of indigestion with fermentation differ but little from those of mild cases of infectious diarrhea. In both instances toxic substances, resulting from bacterial growth, are absorbed into the circulation and cause similar symptoms and pathologic changes. In indigestion with fermentation the seat of bacterial activity is primarily and almost exclusively in the intestinal contents, while in infectious diarrhea it is primarily in the intestinal wall itself. The bacteria do enter the intestinal wall and produce definite lesions of the wall. It is probable that they often pass through the wall into the circulation in infectious diarrhea. The serum agglutination test, as described by Davison,[1] is most useful in making a definite diagnosis in obscure cases, and in determining the exact type of the offending micro-organism. The micro-organisms which have been associated with infectious diarrhea are the various strains of dysentery bacillus, the gas bacillus, streptococcus in its various strains, and the Bacillus pyocyaneus. The type of organism producing the disease varies in different localities, and probably varies each summer. The Flexner type of dysentery bacillus has been by far the most common type seen in Boston during the past few summers. The gas bacillus

[1] Johns Hopkins Hospital Bulletin, vol. xxxi, p. 353.

may be a causative factor in some instances, but as it is frequently found in the stools of infants who do not show the symptom-complex characteristic of infectious diarrhea its presence in infectious diarrhea may be merely a coincidence.

Infectious diarrhea runs a course not unlike typhoid fever, and I believe that the feeding of babies having infectious diarrhea should be governed by the same principles that govern any acute infection. Our aim in feeding, therefore, should be to nourish the patient as well as possible in order to increase his power of resistance against the infection. How this aim is carried out in practice depends on the digestive peculiarities of the individual infant. In infants the disease is complicated by different forms of digestive disturbances, and our management of the feeding should be that of any difficult case of infant feeding. We give the infant what we think it can digest, and we alter the composition of the food to meet the indications as they arise. Lactic acid milk and Eiweiss milk are useful in these cases because they are comparatively low in fat and the casein is in a finely divided and easily digested form. In older children starches should be added early in the course of the disease.

If the baby or child is toxic and dehydrated, the first aim should be to replace the fluid. If it is impossible to give water by mouth, then intraperitoneal infusions should be given, these as often as it seems necessary. The baby should be started on a food low in fat, fairly high in carbohydrate, and a moderate protein, preferably in the form of lactate of casein, which is finely divided and easily digested. The fairly high carbohydrate is used on the assumption that the organisms produce harmless substances from carbohydrates and toxic substances from protein, and that the organisms act and use up the carbohydrate material before they attack the protein.

During convalescence the food should be increased according to ordinary principles of feeding. Bismuth, salol, and other preparations of a like nature have little or no affect on infectious diarrhea. It disturbs the patient to take them and interferes with the administration of food and water, which is a most important factor. Paregoric and other preparations of opium

are, on general principles, contraindicated in all forms of diarrhea, because their action is to diminish the number of movements by depressing peristalsis and not by relieving the cause of the increased peristalsis. The increased peristalsis is nature's effort to get rid of the poisonous intestinal contents. Nature's effort, therefore, must not be interfered with. In infectious diarrhea of the dysenteric type, however, when there is a very large number of small movements accompanied by pain and tenesmus, which prevent the patient from getting rest, it is allowable to give paregoric to diminish the excessive peristalsis and to quiet the patient. There is no danger, if proper care is used, of doing harm by retaining the intestinal contents too long.

CLINIC OF DR. LEWIS WEBB HILL

JUNIOR ASSISTANT VISITING PHYSICIAN TO CHILDREN'S HOSPITAL

I. LOBAR PNEUMONIA WITHOUT PHYSICAL SIGNS. II. NON-TUBERCULAR INFECTION OF THE TRACHEO-BRONCHIAL LYMPH-NODES

I SHALL show you today two rather unusual and interesting respiratory conditions.

CASE I

This baby at birth weighed 8¼ pounds. He was fed on the breast entirely for one month, and since then has taken mixed breast and bottle feedings. He has done very well with his feeding, and up to his present illness never has been sick. He weighs 23 pounds. His illness began as follows:

About a week ago he began to be feverish and vomited once or twice. He has had fever off and on ever since, which has varied between 101° and 104° F. He is very uncomfortable at night and his mother says that he scarcely sleeps at all. He pulls at his ears a great deal, and is also cutting several large teeth which have considerably irritated his gums, and which seem to bother him a good deal. He has had for the last few days a slight rhinitis and coughs occasionally. His family doctor first saw him November 17th. He was first seen by me November 23d.

Physical Examination.—Temperature 103.4° F. The child is alert and active, and seems uncomfortable, but not seriously sick. The throat is slightly red. There are no enlarged lymph-nodes. The tonsils are not enlarged or swollen. The heart is negative. The respiration is not rapid, and the lungs show

no dulness, abnormal breathing, or râles. The abdomen is negative. Both ear drums are considerably reddened and slightly bulging.

Diagnosis.—The diagnosis seems perfectly clear. The fever, the discomfort, the appearance of his ear drums, and the way he pulls at them indicate that his trouble is due to otitis media. Both ear drums were incised November 23d, and a good prognosis was given. He was next seen November 25th, and was no better. His ears had discharged very little and his temperature had been running between 103° and 105° F. Nothing else could be found on physical examination to account for his fever except his slightly discharging ears, and there scarcely seemed enough trouble in the ears to make him as sick as he was. It was decided to take him into the hospital and to keep him under observation. Pneumonia was considered in the differential diagnosis, but his respiration was not rapid and there was never anything abnormal to hear in the chest. His temperature continued elevated and not until December 1st was there noticed a slight amount of dulness high up in the left axilla, not accompanied by râles or bronchial breathing. An *x*-ray of the chest was taken and a very definite patch of pneumonia was seen (Fig. 269).

As I show him to you today (December 2d) you will notice that he does not look like a baby who has pneumonia; his respiration is not rapid, he is breathing with no difficulty whatever, he coughs very little, and his color is excellent. As we examine his chest we find that there is a very slight amount of dulness high up in the left axilla, and we hear a rare, fine, crackling râle. There is certainly no evidence of massive consolidation. His temperature today is 104½° F.

Discussion.—This baby represents a not unusual type of case in infants and children; lobar pneumonia giving no physical signs for the first few days. Of course, it is impossible to tell, in this particular case, how long the baby has had pneumonia, but the chances are that he has had it for a number of days. The probable cause of his temperature and discomfort ten days ago was the ear condition, but the pneumonia must have

developed since then and has been keeping up his temperature. We usually think of pneumonia in infancy as giving rise to very rapid respiration, but this is by no means always so, especially in certain cases where only a small portion of the lung tissue is

Fig. 269.

involved. We must always consider pneumonia in the differential diagnosis when any child has a sustained high fever without physical signs, whether or not the respiration is elevated. This type of pneumonia is most likely to occur high up in the

axilla, as it did in this case, and the consolidation takes the form of a small triangle with the base of the triangle lying in connection with the pleura and the apex pointing toward the mediastinum. It was formerly thought that this type of pneumonia started in the central portion of the lung and it was called a "central" pneumonia. We now know that this is not correct, and that pneumonia probably does not ever start in the central portion of the lung, but almost always at the periphery, and then extends in toward the hilus. The reason why we are likely to get no physical signs of consolidation in this type of case is that in the early stages especially, when the triangular area of consolidation is small, there may be air between the apex of the triangle and the hilus of the lung. Such an area as this, of mixed solid tissue and tissue containing air, does not transmit the bronchial voice sound as well as does solid tissue alone. This has been especially brought out by Mason,[1] and several years ago in his analysis of a series of 30 or 40 cases of pneumonia in children, all showed that the process almost invariably started at the periphery of the lung and extended toward the hilus in the form of a small wedge. This type of case is of especial interest from the diagnostic standpoint, and is not at all uncommon. The Roentgen ray is, of course, of immense value in diagnosis before characteristic physical signs make their appearance.

Figure 269 shows very well the small wedge-shaped area of pneumonia high in the left axilla. At the time this plate was taken physical signs had made their appearance, and undoubtedly if we had had a plate two or three days ago the consolidated area would have appeared much smaller.

CASE II

The next child represents a somewhat different condition. She is four years old and has the following history:

Family History.—Two miscarriages before the birth of this child. No other children in the family. Her mother's sister has had tuberculosis for several years and is an assistant in

[1] Amer. Jour. Dis. Child., vol. xi, 1916, p. 189.

a tuberculosis class. She does not live in the same house with the patient, but the child sees her a good deal.

Past History.—She has always been well except for rather severe intestinal indigestion at two years, which lasted for four or five months, and influenza during the epidemic, two years ago.

Present Illness.—Four weeks ago she had chickenpox and was rather severely sick with it. This was followed by a severe cough, which has kept her awake at night most of the time. It is a rather racking cough, but has not been at all spasmodic in character, nor does she vomit or raise anything after coughing. Her mother says she is getting no better, and her temperature is ranging from 101° to 102° F. every day. She has had several severe night-sweats during the last week.

Physical Examination.—A well-developed girl who has probably lost some weight. I think you will agree, from the character of that cough she just gave, that the cough is more than a simple throat irritation and would be described, perhaps best, as a "brassy" cough, that is, it sounds deeper down than the throat, but sounds somewhat differently from a bronchial cough or from that of pneumonia. The child's throat is slightly reddened, but the tonsils are not large and no mucus or pus is seen on the pharyngeal wall. I think you will all agree that we cannot blame this rather innocent looking throat for such a severe and such a persistent cough, and the chances are that her throat is slightly red, more from the coughing than that the red throat is the cause of the cough. There is no enlargement of the cervical glands. The lungs show no dulness, no bronchial breathing, or no râles. She has a markedly positive D'Espine's sign through the fourth dorsal vertebra, and, if you listen to her, you will see that this is as clear a D'Espine's sign as you have ever heard. The D'Espine's sign, you will remember, is elicited by listening with the stethoscope over the dorsal and cervical spines in the back while the patient says "one" or "thirty-three." If a whisper-like prolongation of the voice sound is heard lower down in the back than the seventh cervical or first dorsal vertebræ, the sign is positive, and indi-

cates the presence of some sort of solid tissue in the mediastinum, in children usually enlarged glands, either tubercular or non-tubercular.

Diagnosis.—The diagnosis of this case is not at all simple. The child evidently has no bronchitis, nor can she have any pneumonic process to account for her cough. Neither have we found in the lungs any physical signs which would suggest pulmonary tuberculosis. Her throat we can undoubtedly rule out as a cause of her cough, as I said before. Can it be that this is simply a nervous type of cough and that it does not rest upon any definite pathologic basis? This would hardly be considered on account of her temperature and general appearance. The positive D'Espine's sign gives us the clue and I think we can make a diagnosis of enlargement of the tracheobronchial lymph-nodes as a cause for her cough. The "brassy" character of the cough is also in favor of this as an etiologic agent. It is not difficult to decide that her cough is due to this cause, but it is quite another question what has caused enlargement of these nodes. It is not possible to say, from the physical examination or from her history, whether her infection is tubercular or non-tubercular in character. The general character of the cough and the history of exposure are perhaps in favor of tuberculosis, and against it is the rather acute onset. There are three additional diagnostic procedures which should help us: (1) The white blood-count; (2) the von Pirquet test; (3) Roentgen ray examination of the chest. Her white blood-count is 11,400. The von Pirquet was done two days ago and was absolutely negative. Her *x*-ray plate, which I will show you, shows considerable congestion in both lung roots and a certain amount of enlargement of the tracheobronchial nodes, especially on the left (Fig. 270). It does not look especially like tuberculosis, as in a tubercular process we would expect to see more calcified glands. The white blood-count in this particular case does not help us very much, one way or the other, although it is a little high for tuberculosis. The negative von Pirquet test is of the very greatest value, and I think it is possible, in view of a negative test in such a case as this, where there is no evi-

dence of overwhelming infection, to rule out tuberculosis entirely as the cause of this girl's symptoms. She probably has a low-grade infection of the lung roots and of the tracheobronchial

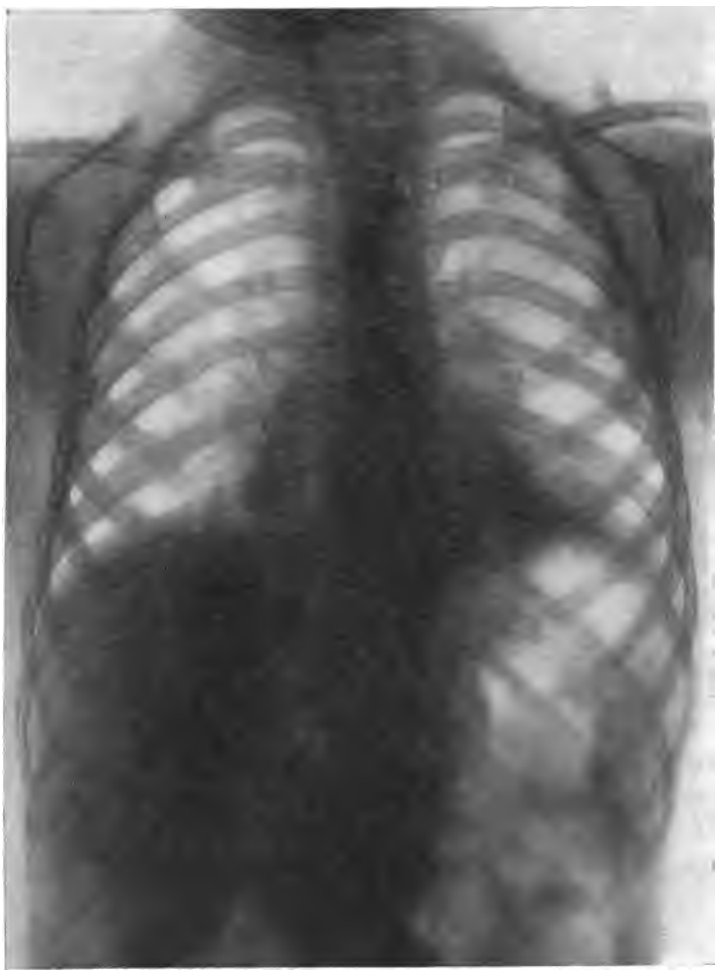


Fig. 270.

lymph-nodes, very similar to some of the infections seen two years ago during the influenza epidemic. The chances are that she will do perfectly well, although she probably will cough somewhat for some time.

As far as treatment goes, we shall keep her in bed as long as she has any fever and will give her 10 grains of sodium bromid every night before going to bed, and small doses of codein during the night if her cough becomes very irritating. She will probably cough less if she has warm air in her room at night than if her windows are kept open. This is a rather atypical case and does not fall into the ordinary category of the usual respiratory infections seen in childhood.

CLINIC OF DR. STANLEY COBB

MASSACHUSETTS GENERAL HOSPITAL

A CASE OF EPILEPSY WITH A GENERAL DISCUSSION OF THE PATHOLOGY

ON December 16, 1921 this patient, aged twenty-nine, male, No. 246,910, was admitted to the Massachusetts General Hospital with a diagnosis of "epilepsy (of questionable Jacksonian type) and chronic otitis media of left ear."

Family History.—The patient's father died of a lung abscess. The mother is living and well and two sisters and one brother are living. The paternal grandmother was "subject to epilepsy," but other than this the family history was negative. There was no history of tuberculosis, insanity, alcoholism, and other diseases.

Marital History.—Always single. Sexual habits unknown.

Occupational History.—The patient was a slow worker prior to five years ago. Since then he has been unable to work on account of epileptic seizures.

Habits.—No tea or coffee; 60 cigarettes a day; uses a little beer.

Past History.—The patient was born in Russia and went to school there until he was twelve years old. After he left school he did not go to work, but helped his mother in her leather store whenever he felt like it. The only illness he had in childhood was measles. In 1910, when he was seventeen years old, he came to the United States and lived with his father, working in factories and at various odd jobs and never sticking long at one job. In 1912, while working as a button-hole maker, he began to have his first dizzy spells. These made him nervous

and were the cause of his visiting the Psychopathic Hospital. From there he was sent to Worcester, where he stayed two months. Sometimes he would wander away during these dizzy spells and not know where he was. On August 28, 1913 he was found unconscious on the street and taken to Danvers' State Hospital, where he stayed three months. He went home for two weeks and then went back to Danvers, and says he has been there several times since. He has visited the Out-patient Department of the Massachusetts General Hospital at irregular intervals from November 30, 1912 to February 6, 1919. A brief summary of the various hospital reports and physical findings is set out below under topographic headings:

Head.—Patient reports vertigo before mastoid operation in 1913 and in 1917. Headache in 1913 and severe headaches for the past four or five years. Tenderness over the right side of the head, in front of the ear, was noticed in 1913. At an examination at the Eye and Ear Infirmary in 1913 the question of brain abscess was considered.

Eyes.—In 1913 the patient had marked exophthalmos, reported to be more on the right than on the left. In 1913 an eye examination at the Eye and Ear Infirmary reported the fundi normal. In 1918, while a patient in the Male Medical Out-patient Department at the Massachusetts General Hospital, the findings at eye examination were: Hemianopsia; pupils small and react sluggishly to light, the right being irregular; marked bilateral exophthalmos. At an examination at the Psychopathic Hospital in 1918 his visual fields were reported contracted.

Nose.—Adenoids removed at Eye and Ear Infirmary in 1920.

Throat.—Tonsils removed at Eye and Ear Infirmary in 1920.

Ears.—Otitis media in childhood. In 1913 pain and deafness in left ear, with diagnosis of chronic suppurative otitis media with granulations. Left mastoid operation at Eye and Ear Infirmary in 1913 and at New York Jewish Hospital in 1920. Patient visited Eye and Ear Infirmary at intervals between these two periods, complaining of ear trouble. Ringing in right ear.

Teeth.—Four missing; some carious. Alveolar abscess with operation in 1912.

Neck.—Negative. Thyroid palpable, not enlarged.

Chest.—Expansion greater on right than on left. Bulging on left posteriorly.

Cardiorespiratory.—Negative. Blood-pressure, systolic 115, diastolic 83.

Gastro-intestinal.—Appetite poor. Diet irregular and inadequate. No constipation. Appendix removed in 1918.

Genito-urinary.—Negative except for small mass in scrotum at left of junction with penis.

Extremities.—Great toes deformed.

Nervous System.—See Present Illness.

Present Illness.—The patient was in the Psychopathic Hospital in 1912 for "nervousness" caused by dizzy spells. Here the examinations showed slight Romberg to left, slight tremor of tongue and hands, and left dorsal scoliosis. Co-ordination tests poorly done. Knee-jerks sluggish, but present. The gait showed some initial ataxia when he was asked to walk toward a person, but he corrected this almost immediately and did not tend to walk in a circle. He did not show this ataxia when walking backward. Wassermann negative; cerebrospinal fluid negative. Rather silly expression and responds stupidly. Psychologic examination: Mental age of 9.3 years with non-English norms. Diagnosis at Psychopathic Hospital: "Not insane, epilepsy. Feeble-minded. Some question of hysteria."

Later he was sent to Worcester and then to the Danvers State Hospital. His first convulsion occurred in September, 1916, when he was working in a shoe factory. He fell to the floor and was taken home. This was followed by one or two a week for three months, and then none for nine months. In September, 1917 he had a series of nearly continuous attacks in a lapse of several hours. In these attacks the patient would fall over, froth at the mouth, and throw his hands and feet about. Each attack lasted about half an hour and he appeared to "see things" after them. He had times (whether in connection with a convulsion or not it was impossible to learn) when he would

say: "I hear something that nobody hears, and I see something that nobody sees." Says that he sees a man with a big knife who wants to kill him. Sometimes he feels something moving in his head. The seizures usually take place in the daytime, but sometimes at night. No headache; no vomiting. In the fall of 1917 he went to Danvers, but they would not keep him. At Danvers an attack was described as follows: "He was sitting further down in the chair than I am, head raised on the back; there were generalized convulsive movements; eyes open; he was not frothing at the mouth, nor did he bite his tongue; he continued in this for some minutes, nor was I successful in rousing him." Patient's description of aura: "I feel bad and my eyes get stuck and I can't see anything." The diagnosis at the Psychopathic Hospital in 1918 was that he was primarily epileptic with some elements of hysteria and psycho-analysis was recommended. It was a question of whether to class the case as a generally functional one with certain organic appendages or as primarily epileptic with certain functional appendages. It was agreed by all that he was primarily a feeble-minded man.

The patient was in the Male Medical at the Massachusetts General Hospital for a period in 1918 on account of his convulsions, and at that time was having about two attacks a day. His appendix was removed at this time, but there was no amelioration of the convulsions. In February, 1919 he was referred to the Nerve Clinic at the Massachusetts General Hospital on account of his convulsions and was advised to go to the Munson State Hospital.

On December 15, 1921 the patient had an epileptic attack while visiting a friend on Ward 30 at the Massachusetts General Hospital and was kept as a patient. He complains of severe headache and diplopia since his entrance and says he feels very weak.

Physical Examination.—Well developed and nourished.

Head.—Receding forehead. *Mucous membranes* normal. *Eyes:* Marked exophthalmos and stare; scleræ clear. *Ears:* Negative. *Left mastoid*: Large scar. *Nose:* No obstruction; septum intact. *Teeth:* Many carious, showing pyorrhea, but

no lead-line. *Tongue:* Marked white coat; extended in midline with no tremor. *Throat, neck,* and *thyroid* all negative. *Tonsils* excised. *Glands:* Inguinal and lymph-nodes enlarged.

Thorax.—Chest well developed, right equal to left. *Breast* negative. *Spine* negative. *Diaphragm expansion:* Right equal to left.

Heart.—Apex impulse not seen. Sounds regular, not rapid; good quality. $P_2 = A_2$. Artery walls not palpable. *Blood-pressure* 90/60.

Abdomen.—Level, with no masses, spasm, or tenderness; soft and tympanitic. *Liver:* Dulness from fifth rib to costal margin. No *costovertebral tenderness. Spleen* negative. *Kidneys* negative. No edema.

Rectal negative.

Neurologic Examination.—*Cranial nerves* are negative except that the fundi were possibly slightly abnormal (as noted below in the consultation note). There was no facial weakness (some convulsions began on the left side of the face, whereas others began on the right). The *motor system* could not be examined satisfactorily because the patient was in bed on account of his frequent convulsions. The position of the left hand and arm, however, was striking; this limb was partly flexed at the elbow and the hand was held in the position of tetany (the fingers drawn together and the wrist flexed). There was marked weakness in the muscles of the arm, forearm, and hand, and unsteadiness in performing any motion. The mother states that after attacks this weakness of the left hand is more marked than between attacks, and that the left leg is also weak, especially after attacks. No asynurgia was made out except in the left hand. The deep *reflexes* were all hyperactive and approximately equal on the two sides. There was no clonus. The right foot showed a normal plantar reflex and the left a questionable Babinski. The abdominal reflexes were normal. A satisfactory *sensory* examination was impossible, but nothing abnormal was made out. The *autonomic system* showed instability, *e. g.*, exaggerated skin reactions, flushing, low blood-pressure, and easily dilating pupils. At the time of the examination the right pupil was greater than the

left, both were circular and reacted to light and accommodation. There was no evidence of abnormality in the *endocrine system* unless the exophthalmos might possibly be considered as related to the thyroid.

Laboratory Examinations.— *Urine* negative. *Blood:* An examination on December 17th showed a white cell count ranging between 6900 and 8700 and a normal red cell count; hemoglobin, 80 per cent.; lymphocytes, 25 per cent.; large mononuclears, 7 per cent., and basophils, 1 per cent. On December 21st the white cell count was 14,200. The Wassermann reaction on the blood was negative. Non-protein nitrogen was 54 mmg. per 100 c.c. Blood CO_2 was 57.2 volumes per cent. *Spinal fluid:* 10 c.c. of clear, colorless fluid were withdrawn; the pressure was 90 mm. of spinal fluid in the 1 mm. bore manometer; after withdrawing a second 5 c.c. the pressure reading was 30 mm. Cell count: 1 per cu. mm. Ammonium sulphate: 0. Alcohol: normal. Wassermann negative. Total protein: 73 mgm. per 100 c.c.

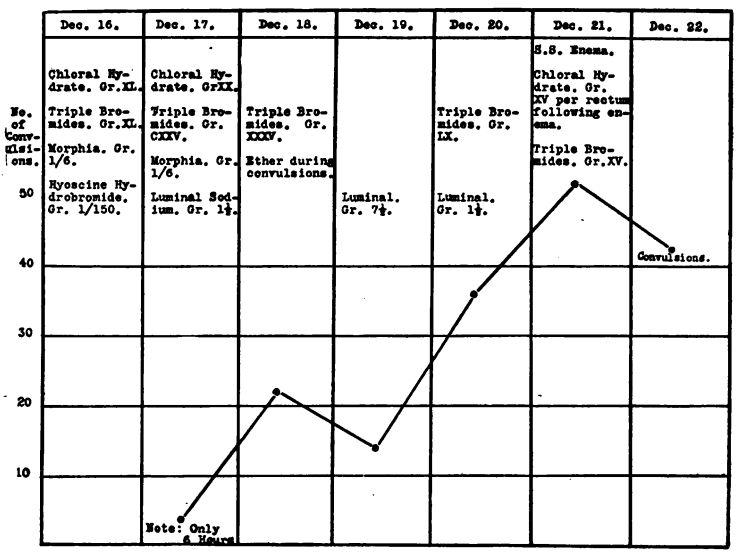
The patient ran a *fever* of 99° F., except on the 17th, when it rose to 100° F., and on the 20th and 21st, when it rose to 101° F. His *pulse* was between 70 and 80, except on the 17th, when it went up to 90, and on the 20th and 22d, when it rose to 110. The *respiration* was 15 on the 16th, 25 on the 17th, 30 on the 21st, and a little above 30 on the 23d.

Note on December 21, 1921: In view of increasingly severe convulsions a right osteoplastic exploration is suggested, to be performed as soon as possible.

December 23, 1921. Ear Consultation: There is a profuse mucopurulent discharge from the high posterior perforation, through which a polyp bulges. There is no evidence of radical mastoid operation. Tenderness and pain are found above and around the left ear.

Neurologic Consultation: The fundi are probably within normal limits and, although the disk edge on the right suggests an old optic neuritis, there is certainly no evidence of increased intracranial pressure. No complete paralysis of limbs is discovered and all reflexes are within normal limits. The position

of the left hand is striking, but it does not impress me necessarily as the result of cerebral pathology. There is no astereognosis. It seems that evidence for abscess, either cerebellar or temporal, is very slight. In view of the left ear condition I would recommend a thorough investigation of this, including exposure of the dura, but not the opening of the dura at the first operation. This work had best be done by the aurist. *Neurosurgical note:* While none too positive as to causation or localization, it would seem as though the right motor cortex might



Convulsions and Medication from Dec. 16th to Dec. 22nd.

Fig. 271.

reveal some pathology and an osteopathic flap exploration is advised as soon as possible.

The accompanying chart (Fig. 271) shows the number of convulsions per day and the medication in relation to the convulsions. Descriptions of a few of these attacks follow: December 18th at 7.45 A. M.: Convulsion. Severe shaking for half a minute. The eyes are rolled upward and jaw is clenched hard on gag for a minute and a half more, with hard swallowing. 8.05 A. M.: Convulsion. Severe shaking for twenty seconds and

frothing and hard breathing for fifty seconds. He went into another convulsion before recovering from the first one. Severe shaking for ten seconds and frothing for twenty seconds. He was very flushed and felt "all gone" afterward. 12.45 P. M.: Convulsion; ether administered and it shortened the rigid and shaking stage, but lengthened the stage of complete recovery of consciousness and produced much more mucous and some gagging and coughing. 6.30 P. M.: Talks somewhat irrationally at times. Convulsion, which lasted three minutes. A second convulsion followed in less than a minute.

December 23, 1921: Transferred to Eye and Ear Infirmary. A convulsion witnessed began with a spasm of the left side of the mouth and face and extended to the jaws and extremities. The convulsions were at first tonic and then became clonic in character, and lasted about a minute altogether. The eyes were strained upward and to the left. After the convulsions subsided the extremities remained in tonic spasm.

December 24, 1921: A left modified radical mastoid operation was performed under ether. A postaural incision was made anterior to the scar from the previous mastoid. The cortex was hard and intact for 1 inch in width back of the meatus. Posterior to this there was a large area of exposed dura not covered by bone and bounded by sharp, irregular edges. The mastoid was densely sclerosed. A modified radical was performed. The facial ridge was not greatly taken down. Kormer flap. The bone edges of previous decompression were trimmed and the dura incised with a small, straight incision. On probing, there was failure to locate pus; 00 catgut stitch in dura. Rubber-dam drain. Three sutures.

December 24, 1921: Temperature, 99° F.; pulse, 85; respiration, 23.

December 25, 1921: Temperature, 102° F.; pulse, 109; respiration, 20.

December 26, 1921: Temperature, 100° F.; pulse, 80; respiration, 32.

December 27, 1921: The rubber drain and its stitches were removed. The patient has been kept in the strong room with a

special nurse since his admission. He has improved steadily. His temperature, pulse, and respiration are about normal, and he is apparently rational. He has had two attacks of very slight intensity which were chiefly facial contortions. He was up tonight.

December 29, 1921: The patient was moved to the main ward and put on ordinary diet. The wound is healing well and the patient is rational.

January 1, 1922: The patient is up.

January 2, 1922: The iodoform was removed and the cavity filled with boric acid. The patient has had no fever for two days and his general condition is good. He has had two more spasms, apparently of intention.

January 8, 1922: The wound has been dressed and filled with boric acid daily and is now reduced to a small hole. There has been no reaction; he is up all day, looks well, and has no fits.

January 13, 1922: The patient's wound is closed and dry.

January 14, 1922: The wound is closed, dry, and depressed. Middle ear drying. He is getting fat and looks well and has had no fits in twelve days. Discharged improved to the Out-patient Department.

March 1, 1922: Seen in Out-patient Department, where he reports that since leaving the hospital on January 14th he has had frequent bad headaches and about two convulsions a week. Some of these have been while he was in bed, usually early in the morning; a few have been during the day.

Neurologic Examination.—All the *cranial nerves* are negative except for the eye-grounds, which are as noted above. The *motor system* shows a marked weakness of the left arm and hand; when extended there is tremor of the fingers, and the left hand and the left arm cannot be held up as long as the right. The position of the fingers is that of hyperextension and reminds one of an athetoid hand. The finger-nails are bitten down nearly to the "quick." In walking the patient everts the left leg and scrapes the floor with the inner margin of the left shoe. The left leg appears to be somewhat stiff. The left arm is held slightly flexed and the hand hangs limply on the loose wrist.

The muscles of the left leg are weaker than those of the right. Motions are made unsteadily and he is not able to raise the left leg as quickly as the right in such a test as touching the examiner's finger with his great toe. The deep *reflexes* are all exaggerated, the knee- and ankle-jerks being, perhaps, slightly greater on the left than on the right. In the right foot the plantar reflex is normal; in the left it is difficult to obtain and sometimes suggests Babinski's phenomenon. No *sensory* abnormalities were made out. *Autonomic* and *endocrine* systems as at former examination.

DISCUSSION

We have in this case a complex picture, as indicated by the varied opinions expressed in the notes by consultants. There was little unanimity as to etiology or treatment. Brain abscess and meningitis were considered as possible irritating factors by those who laid stress on the middle-ear condition. Others were more struck by the left hemiplegic syndrome, and felt that relief might be achieved by exploration of the right motor cortex. None of us were as philosophic as a trained epileptologist would have been under the circumstances, for only those who have seen epileptics in large institutions know how important the whole history is and how focal symptoms may appear in patients with general convulsions, in contradistinction to those cases showing focal lesions at autopsy when no neurologic signs indicated their presence before death. If the whole history had been gathered from all sources and presented chronologically, I doubt whether operation would have been considered seriously by any of us. In the first place it must be noted that the patient has probably always been a feeble-minded individual with a chronic irritation from early childhood in the guise of otitis media. In 1912, at the age of nineteen, he has attacks that may be considered petit mal. In 1913 the exophthalmos is first noted (although it may have been present before this), and in that same year he undergoes an operation on his left mastoid because of the aural infection. In 1916 comes the first major convulsion with unconsciousness, and thereafter he goes from hospital to hospital seeking relief in one way or another from

psycho-analysis to appendectomy. In this last exacerbation, during which we have observed him in the hospital, there is evidence of a focal lesion. This is indicated by the neurologic signs in the left hand and arm which are more marked after the convulsions. The nature of this lesion is uncertain. The otitis

Fig. 272.—Conspicuous degeneration of right corticospinal tract (above decussation). Case N-12-34: Age at death nineteen years. Duration of epilepsy seventeen years. Mental condition, moron. Physical condition: paralysis of left arm and hand; no motion in fingers, no action in forearm; contraction of wrist and fingers. Was said to have had meningitis at two years of age, paralysis of left upper extremity following meningitis. Cause of death, status epilepticus. Autopsy: focal atrophy and gliosis in right hemisphere; encephalitis. This case had general convulsions, but definite paralysis of the left arm, and the illustration shows degeneration of the corticospinal tract.

media might make us consider the possibility of a brain abscess, but none of the symptoms elicited are referable to the cerebellum or temporal lobe of the cerebrum and, although the corticospinal tract might be affected in its passage through the hind-brain, it is usually conceded that convulsions of this sort arise from irri-

tation of the cerebral cortex and not of the tract. The symptoms strongly point to pathology in the right motor cortex, although there is evidence that the lesion is secondary and developed years after the onset of the epilepsy. The case, in other words, is one of general convulsions with certain indications of a focal cerebral lesion. It must be remembered that many epileptics

Fig. 273.—Degeneration of right corticospinal tract and atrophy of right lateral column of cord. Case N-10-90. Age at death eighteen years. Duration of epilepsy twelve years. Mental condition, imbecile. Physical condition: partial paralysis of right side with slight atrophy; paralytic gait; muscular co-ordination fairly good; knee-jerks exaggerated. Cause of death, status epilepticus. This case also had general convulsions in spite of the obviously focal lesion.

whose brains show diffuse changes have neurologic symptoms indicating focal lesions in the cortex; thus the line between "Jacksonian" or focal convulsions and general convulsions seems to be an indistinct one. The lesions in Jacksonian epilepsy are more obviously focal, and all cases showing the true Jacksonian syndrome with its "march" of the convulsion should be surgically explored, but cases showing only partially focal con-

vulsions without the "march" of symptoms are most misleading and generally have wide-spread lesions which could in no way be benefited by operation. Examples of those cases of epilepsy with a history of general convulsions from the onset, but with neurologic symptoms indicative of focal lesions in the brain are often found (Figs. 272–274). These may appear to be somewhat focal; the first twitches may often be in certain muscles, and one side of the body may be more involved than the other,

Fig. 274.—Chronic meningo-encephalitis. Case N-22-26: Age at death fifty years. Duration of epilepsy twenty-eight years. Mental condition, progressive deterioration. Physical condition: Reflexes normal; progressive bilateral neuroretinitis with limited vision. Cause of death, status epilepticus. Autopsy: Focal atrophy along the frontoparietal region in the right hemisphere and the parietal region in the left, with chronic leptomeningitis and adhesions to the dura. Microscopically there was marked gliosis and evidence of an old encephalitic process.

but, when carefully observed, these signs will be found to be variable, the definite "march" is lacking, and there are no positive neurologic signs. Such cases may show *no* focal lesions, merely diffuse pathology. The usual findings in the Jacksonian type are small tumors, adhesions with arachnoid cysts, or vascular lesions, but these focal lesions can give general convulsions.

A general belief is that there is no definite pathology in the brains of epileptics. This is true to a certain extent—there is

no *specific pathology* found in all such brains. But a great many epileptics have distinctly pathologic brains even if some brains of epileptics show no lesions. Two-thirds of one series (Fig. 275, autopsy findings) and three-fourths of the other showed gross brain pathology, while the search for microscopic pathology disclosed gliosis in well over half of the cases.

From another angle the figures of Lucas and Southard[2] are interesting. They followed 12 cases of polio-encephalitis for six years after the acute illness: Two died and three became epileptic.

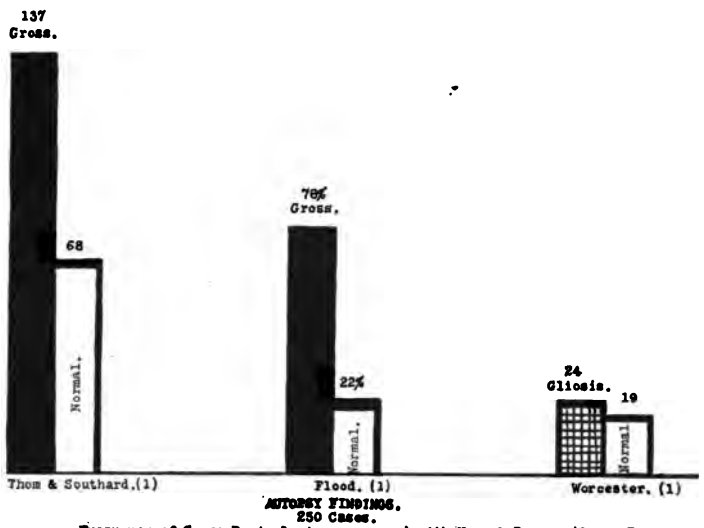


Fig. 275.

Conversely, some cases of supposed "idiopathic epilepsy" show lesions of old meningitis or encephalitis at autopsy.

From another angle we can approach this subject—the effects of trauma on the brain. Frazier and Ingham[3] report 176 cases of gunshot wounds of the head. Within about a year 28 of them developed convulsions, and it is interesting to note that although the lesions must all have been focal, there were nearly as many general convulsions resulting as focal.

Thus there seems to be no sharp distinction between the

obviously organic focal epilepsy and the "idiopathic" without lesions discoverable at autopsy. We can have focal lesions with focal convulsions, or with focal convulsions spreading to become general, or even with general convulsions. We can have diffuse lesions with general convulsions, or somewhat focal (though variable) convulsions. And we can have convulsions with no discoverable lesion.

The fact that Frazier and Ingham[3] found wounds of the parietal region causing convulsions more often than those of other

Fig. 276.—Case N-15-42. Whole-brain section showing microcephaly and microgyria in an infant dying in status epilepticus.

parts of the cortex is interesting in view of Southard's theory of "epileptogenic foci"[4]—areas in the cortex where lesions with gliosis have cut off association tracts and caused abnormally simplified reflex arcs. Over these arcs it is conceivable that uncontrolled discharges may pass easily and cause epileptic phenomena. It might theoretically be expected that lesions in the sensorimotor cortex of the parietal lobe would be especially likely to set up convulsions.

Further evidence that "simplified arcs" tend to cause epileptic motor discharges is found in the feeble-minded. Here we have much epilepsy among the lower grades, and these cases have more or less simplified brains, with a characteristic lack of association fibers. For example, Case N-15-42 (Fig. 276) is an infant with microcephalus and microgyria, who died at the age of two years in status epilepticus.

In certain cases of epilepsy, with or without gross pathology, we find heterotopia, *i. e.*, a congenital condition of misplaced and abnormal nerve-cells. Examples are found in the cortex of the cerebrum and cerebellum, and even in the white matter at a distance from the cortex. These cells are often embryonal in type. Similar abnormalities may be found in the feeble-minded.

It has often been stated that epileptics show many "*stigmata of degeneration*," *e. g.*, webbed fingers, abnormal ears, certain facial types, special cranial characteristics, etc. The figures of the Massachusetts State Hospitals, however, indicate that there are fewer of these anomalies found in epileptics than in most psychoses, less even than in senile dementias and about the same percentage as in paresis. So it seems probable that epileptics, excluding the feeble-minded, have no more of these stigmata than average non-epileptic people.

It is also a common belief that epilepsy is a strongly inherited disease. Older writers state that the positive-inheritance histories run as high as 50 or 60 per cent.; but more recent and, I think, more reliable work[5, 6, 7] puts the percentage of positive family histories at the low figure of 4 to 6 per cent. My explanation of these discrepancies would be that feeble-minded individuals with "simple brains" are particularly liable to have epilepsy and that the earlier investigators did not exclude these cases. We know that feeble-mindedness is strongly inherited, and therefore cerebral aplasia may account for a large percentage of inherited epilepsy. But the autopsy findings in cases of imbecility are so often not aplasia, but infection of the brain, that we should be careful not to be dogmatic.

The fact that children are so much more prone to convulsions than adults is perhaps explainable on the theory of "simple

brains" and simplified reflex arcs which can easily conduct abnormal motor discharges, for children's brains are not fully myelinated, complete development in this respect not taking place until the sixteenth or eighteenth year.

Turning now to experimental work, all the evidence seems to indicate that the origin of convulsions is in the cortex and more especially in the motor cortex. Quite similar convulsions can be produced by stimulating lower centers, or by stimulating animals with the higher centers removed, but the stimulus needed to produce convulsions in these animals with reduced nervous systems is considerably greater. For example, in our laboratory we have been using wormwood oil (the essential oil of absinthe) and thujone to produce convulsions in rabbits. We find that an intact animal will have a severe convulsion after intravenous injection of 1 c.c. of a 1 per cent. solution of thujone, whereas decerebrate and spinal animals will need two or three times the dose. But sufficiently large doses will produce similar convulsions. The cortex is, therefore, not the only locus from which convulsions can arise, but it is probably the locus most easily set off.

What attitude, then, should we take toward the pathology of epilepsy after studying such a case as the one here presented and after such a discussion? It would seem, in the first place, that more cases of epilepsy have meningitis, encephalitis, or traumatic lesions than we realize. Second, that more clinico-pathologic correlation is needed to clarify our ideas about the relationship of epilepsy to feeble-mindedness, to inheritance, and to the infections of childhood. Third, that more thorough autopsies must be done, and more experimental work carried out, to throw light on gliosis, especially as to whether it is to be considered a cause or an effect of the convulsions. In conclusion, it seems that Southard's idea of epileptogenic foci is the best theory yet promulgated to explain the mechanism of convulsions, but even this theory throws no light on the etiology.

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CLINIC OF DR. CHESTER M. JONES

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A STUDY OF THE BILE PIGMENTS BY MEANS OF THE DUODENAL TUBE IN A CASE OF PAROXYSMAL HEMOGLOBINURIA

THE present wide-spread interest in the use of the duodenal tube as an aid to diagnosis and treatment of biliary tract disturbances dates from the introduction of the so-called Lyon-Meltzer method of "non-surgical biliary drainage." Since the appearance of Lyon's original work numerous investigators have attempted to study and analyze biliary tract pathology by duodenal analysis. The previous work of Einhorn and others demonstrated the possibility of obtaining and studying the contents of the duodenum, but a profuse and relatively long-continued flow of bile into the duodenum as a basis for careful analysis had not been obtained. The use of a solution of magnesium sulphate in the duodenum, following Meltzer's original suggestion in 1917, was introduced by Lyon in 1919. He demonstrated conclusively, in a large series of cases, that the instillation of a solution of magnesium sulphate into the duodenum was followed by an increased flow of bile. This flow of bile was usually profuse and continued at a relatively rapid rate for a half-hour or for even longer periods. Examination of the gross color of the bile showed that the samples obtained could be divided roughly into three fractions, which were designated by Lyon as "A," "B," and "C" bile, the "B" bile being of a much darker color than the other two fractions. Arguing from Meltzer's original suggestions as to the existence of a system of crossed innervation between the muscle-fibers in the sphincter of Oddi and the musculature of the gall-bladder wall and his almost philosophic consideration of the action of

magnesium sulphate when instilled into the duodenum, Lyon concluded that the salt produces a relaxation of the sphincter of Oddi, and at the same time a contraction of the gall-bladder walls. From this hypothesis he further concluded that the light yellow "A" bile is common duct bile, the darker "B" bile is bile coming from the gall-bladder following a contraction of that organ, and the "C" bile is from the hepatic duct and higher biliary radicals coming after the emptying of the gall-bladder.

Too close acceptance of Lyon's conclusions may be misleading, and a careful examination of the facts shows that his hypothesis is based largely on clinical data. Careful experimental evidence is conspicuously lacking as to the presence of gall-bladder contractions following the use of magnesium sulphate in the duodenum. Even if the normal contractions of the gall-bladder are increased by the administration of magnesium sulphate, such contractions must be extremely slight if we are to accept the excellent work of the English physiologists on the normal contractility of the gall-bladder. The importance of this increase in gall-bladder contractions has probably been much overemphasized. Furthermore, in a large proportion of cases the sequence of "A," "B," and "C" bile is not absolutely distinct, and a separation of the three fractions is to some extent artificial and varies with the individual observer. The so-called "B" bile, with its darker color than the "A" and "C" fractions, is due, I believe, to several factors: an increased flow of bile into the duodenum due to a relaxation of the sphincter of the common bile duct, slightly increased gall-bladder contractions, and passive siphonage of bile from the gall-bladder. This fraction, then, probably contains a mixture of liver, gall-bladder, and duct bile. It is difficult, therefore, to believe in the value or necessity of attempting to obtain an accurate segregation of the duodenal contents, following the use of magnesium sulphate, into "A," "B," and "C" biles. A simple fractional analysis of samples taken over definite intervals for an hour or more after the use of the salt will undoubtedly yield equally valuable results.

A similar criticism seems justified as regards too fine a differentiation between the various cellular and crystalline elements in the sediments of the various fractions. Attempts to decide upon the level of biliary tract pathology from the type of cells found in the sediment is probably as fallacious as are attempts to localize genito-urinary pathology by the type of cells found in the urinary sediment. A conservative point of view, therefore, in regard to conclusions based upon duodenal analysis should be maintained, at least until the facts gained by clinical investigation have been more carefully substantiated by experimental work.

The value of Lyon's work should not be underestimated, however, and his method, or some modification of it, will undoubtedly lead to a much more exact understanding of the various disease processes affecting the duodenum and biliary tract. A modification of Lyon's original technic has been employed in this laboratory, with a view to studying the pathologic physiology of various diseases involving either directly or indirectly the biliary tract. The principles involved in this work are not new, and depend upon work previously done by Schneider and others upon the biliary pigments in the duodenum. By combining a study of the bile pigments in the duodenal contents, with a study of the cytology and bacteriology, as outlined by Lyon, a more exact picture of the abnormal physiology existing in any disease of the liver and biliary tract may be obtained than formerly.

Technic.—The technic employed in a large series of cases is briefly as follows: The duodenal tube is introduced into the fasting duodenum, and duodenal contents obtained from the fasting organ in two fractions, each fraction being collected over a period of fifteen minutes. An instillation of 60 c.c. of a 33 per cent. solution of magnesium sulphate is then given through the tube, and as soon as the flow of bile is re-established four subsequent fractions are collected, also over fifteen-minute intervals. In addition to observation of the physical characteristics of the various samples obtained and microscopic examination of the sediment the various fractions are care-

fully tested for the amount of bile pigments contained in each. The pigments normally occurring in human bile, and therefore in the duodenal contents, are bilirubin, biliverdin, urobilinogen, and urobilin. Of these pigments, bilirubin and urobilin occur in definite and fairly large quantities. Biliverdin occurs in small amounts, depending upon the presence of any stasis; urobilinogen, the precursor of urobilin, occurs normally only in traces. Determination of bilirubin and biliverdin can be made colorimetrically by treating the duodenal contents with acid alcohol and reading the resulting blue-green color produced by oxidation against a standard solution prepared from copper sulphate and India ink. This method, which was devised by Whipple and Hooper in their animal experiments upon bile-pigment metabolism, is satisfactory only in cases which do not show marked alteration from the normal. Cases in which there is definite disease of the biliary tract are very apt to present samples of bile which on oxidation show the presence of cholecyanin, which changes the characteristic blue-green color to various shades of purple, thereby preventing any satisfactory comparison with the copper sulphate standard. The pigment urobilinogen and its reduction product, urobilin, are readily identified by spectroscopic examination. The various specimens of duodenal contents are treated with a saturated alcoholic solution of zinc acetate and filtered. By this method bilirubin and biliverdin are removed, and the lower pigments put into alcoholic solution. These solutions are then examined in the spectroscope for the presence of the characteristic absorption bands. Cholecyanin, if present, may also be identified by spectroscopic examination. Values for the individual pigments are arbitrarily taken as the number of dilutions with ethyl alcohol required to remove the characteristic absorption bands. This method, which was applied to the study of the bile pigments in stools by Wilbur and Addis, and others, and later applied to the study of duodenal contents by Schneider, is extremely satisfactory. It does not give an absolute value for the concentration of the bile pigments in the bile, but results obtained by this method give satisfactory approximations

of the pigment level in different individuals, and by such relative figures a satisfactory idea of the level of bile-pigment elimination may be obtained. Furthermore, such a process of examination is obviously much more accurate than any gross estimation of color as indicated by qualifying adjectives such as yellow, golden, yellow brown, green, etc. Repeated examinations by the above method have shown that there may exist marked increases in pigment content in the duodenal contents, without there being a corresponding change in the gross color of the specimen. For purposes of comparison the dilution values of urobilinogen and urobilin were added together, and the total taken as the pigment value of the individual specimen.

Clinical Application.—By means of the above technic, which is substantially a modification of that of Lyon, a series of patients have been studied, principally from the point of view of sediment and bile-pigment changes. For a basis of comparison a sufficient number of normal individuals was observed, both as to cellular and crystalline elements in the duodenal contents before and after the use of magnesium sulphate, and the pigment concentration of the various fractions before and after the use of the salt was plotted. The normal pigment curve, based on the values of urobilinogen and urobilin in the individual fractions, as given in Table I, shows clearly the

TABLE I

Average of Bile Pigment Determinations on a Series of Normal Individuals.

Fraction.[1]	Dilution units, urobilin.	Urobilinogen.	Total.
1	5	0	5
2	24	0	24
60 c.c. of 33 per cent. magnesium sulphate given at this point.			
3	115	4	119
4	70	2	72
5	43	0	43
6	16	0	16
			6)279
	Average pigment level.....		46

[1] Each fraction represents duodenal contents collected over a period of fifteen minutes.

changes in pigment concentration before and after the use of magnesium sulphate and indicates the usual relations between the two pigments. Estimations of bilirubin values normally parallel the values of the lower bile pigments. The peak of the pigment curve is seen normally to occur after the instillation of magnesium sulphate, and corresponds to the "B" bile of Lyon. There is a fairly wide variation in the normal level of pigment elimination into the duodenum, but the average of forty to fifty dilution units, as shown in Table I, offers a practical value for comparison with abnormal cases. By comparison of the normal pigment curve and average with the findings in cases showing pathology in the biliary tract valuable information has been obtained concerning alterations in physiology. Such information, when combined with careful sediment examination, has proved of distinct aid in diagnosing difficult cases with involvement of the biliary tract. Such cases included not only cholecystitis, cholelithiasis, catarrhal jaundice, etc., but, in addition, various types of liver involvement and obscure blood conditions.

As an example of the application of the above method of studying duodenal contents, with especial reference to pigment elimination, the following case of paroxysmal hemoglobinuria is reported:

Study of Case of Paroxysmal Hemoglobinuria.—Paroxysmal hemoglobinuria is a chronic disease due to syphilitic infection, manifesting itself in paroxysms of hemoglobinuria and in characteristic constitutional symptoms. The blood of patients suffering from this disease contains in latent form a specific hemolysin, which becomes active when the blood is chilled and produces the attacks. Chilling of the blood to a temperature below 15° C. causes this specific hemolysin to become attached to the red cells. During subsequent warming at body temperature the hemolysin becomes active through the influence of the complement normally present in the blood and hemolysis ensues. The amount of hemolysis is readily measured by the amount of free hemoglobin in the

plasma, and is dependent upon the length and severity of the chilling to which the blood is exposed.

The pathologic physiology of this rare disease is of interest not only as regards the peculiar condition of the blood found in patients suffering with it but also as regards the disposition of the excessive amounts of hemoglobin liberated during an attack. The close relation between the bile pigments and the hemoglobin during the process of blood destruction is well known. A case of paroxysmal hemoglobinuria, therefore, offered an unusual opportunity of studying the results of blood destruction such as occurs in an attack of paroxysmal hemoglobinuria, and of determining, if possible, the effect of such an attack on bile pigment formation and elimination.

The patient (G. L. T.) who was the subject of this study presented all the characteristic features of this disease. He was a congenital syphilitic. He showed in his blood the presence of the specific hemolysin peculiar to the disease and was subject to attacks of hemoglobinuria on exposure to chilling. The experiment conducted on this patient consisted in the production of an attack of hemoglobinemia with a subsequent study of the pigments in the blood, duodenal contents, and urine. The condition studied was thus essentially intravascular hemolysis uncomplicated by any other factor, such as liver damage, trauma, etc. An attack of hemoglobinemia was brought about by immersing the patient's hands in ice-water for several minutes and then warming the chilled members. Chilling was not severe enough to cause more than a trace of hemoglobin to appear in the urine. Blood for examination was taken from the arm vein into oxalate solution, and the amount of free hemoglobin as determined by spectroscopic examination of the oxalated plasma indicated the approximate amount of hemolysis. Red cell counts before and after the attack of hemolysis was produced also served as a basis for estimating blood destruction. As a further means of determining the elimination of bile pigments in this particular case the blood-plasma was tested at various intervals to determine any increase of bile-pigment content of the blood. This was done by the simple

method devised by Blankenhorn, which compares the yellow color of the oxalated plasma with distilled water. The plasma is diluted with water until the yellow color disappears. The concentration of bilirubin is arbitrarily taken as the number of dilutions with water necessary to cause the disappearance of the yellow color from the plasma. Normally this value lies between fifteen and twenty dilutions. Where the yellow color of the plasma was changed by the presence of free hemoglobin the presence of bile pigment was tested for by the Gmelin test with nitric acid. This test gives a positive reaction only in the presence of relatively large quantities of bilirubin and is never positive in normal plasma.

In this case the duodenal contents were examined not only for the bile pigments, urobilinogen and urobilin, by the spectroscopic method, but, in addition, the method of Whipple and Hooper was employed to determine the relative level of bilirubin. The duodenal contents were obtained and studied prior to the production of an attack and the bile pigment values corresponded closely to the normal curve outlined in Table I. An attack of hemolysis was then produced by immersing the patient's hands in ice-water for several minutes, and duodenal contents were then obtained over fifteen-minute intervals for the next four hours. The tube was then withdrawn, but was reintroduced the following morning in order to determine any subsequent changes. In order to insure a continuous flow of bile small amounts of magnesium sulphate solution were introduced at intervals of about an hour throughout the entire examination.

Prior to the attack of hemolysis the pigments in the duodenal contents were within normal limits. Furthermore, there was a normal amount of bilirubin in the plasma as measured by its yellow color, and the Gmelin test was negative. The free hemoglobin observed in the plasma shortly after the patient's hands had been chilled indicated the immediate destruction of the patient's red cells within the blood-vessels. Comparison of the red cell counts taken immediately before and after the attack of hemolysis showed a drop of about 800,000 red cells

per cubic millimeter. The plasma at this time was bright red and gave no tests for the presence of bilirubin. Twelve minutes after the attack the plasma showed less than one-fourth of the amount of free hemoglobin observed in the previous sample and gave a positive Gmelin test, indicating an excess of bilirubin. Blood taken forty-five minutes after the production of the attack showed a still further reduction in free hemoglobin content, and the plasma was deep golden in color. The Gmelin test was strongly positive. From this point the pigments in the blood gradually returned to normal.

A study of the duodenal pigments showed no increase over the peak of the normal curve previously obtained until one hour after the production of the attack. At this time there was a marked rise in the bilirubin values. This rise in bilirubin content of the bile started at the time when the free hemoglobin had entirely disappeared from the blood, and when the bilirubin of the plasma had already begun to return to the normal level. The bilirubin content of the bile continued to increase until it reached its highest concentration at a point two hours following the attack. From this time it gradually diminished in amount, but three and one-half hours after hemolysis was produced the bilirubin concentration in the bile was still nearly twice the greatest amount obtained before hemoglobin was liberated into the circulation. Urobilinogen and urobilin values also showed a marked increase, but the time of appearance of these pigments was later than that of bilirubin. At the end of two hours, when the bilirubin concentration had reached its peak, urobilin and urobilinogen began to show a definite increase over the normal. From this point, however, they continued to increase until the greatest concentration of these pigments in the bile was reached about three hours after hemolysis had been produced. The highest values for these pigments were more than three times the highest point on the normal pigment curve. Urobilin and urobilinogen then gradually diminished in amount, although about four hours after the induction of hemolysis their concentration in the bile was still more than double the highest point reached in the control readings.

Examination on the following morning of the duodenal contents showed that their bile pigment content was still slightly above the control readings, although this was some twenty hours after the attack of hemolysis had been produced. The blood at this time had returned entirely to normal.

Conclusions.—Analysis of the above findings in this interesting case brings out the following points: Following an uncomplicated attack of red cell destruction in man the hemoglobin liberated into the general circulation was rapidly changed to or replaced by an increased amount of bilirubin in the plasma. There was no demonstrable response in the liver excretion of bile pigments, however, until all the hemoglobin and the greater part of the excess bilirubin had disappeared from the plasma. There was subsequently a marked response on the part of the liver to the sudden excess of pigment in the circulation, as indicated by the elimination in the bile of a tremendous amount of bilirubin. This increase amounted to as much as three times the normal concentration of this pigment in the bile, and is clear evidence of a definite relation between the liberation of hemoglobin into the circulation and the excretion of bilirubin in the bile. Such an increase is also definite evidence of a stimulation of the liver to increased activity by the products of red cell destruction. The accompanying rise in concentration of urobilin and urobilinogen in the bile following the production of an attack of hemolysis indicates the close relation of these pigments to bilirubin, and thus indirectly to hemoglobin. The short interval between the peak of the bilirubin curve and the subsequent rise in urobilin and urobilinogen values in the bile precludes the formation of these latter pigments in the intestine and subsequent absorption via the portal circulation. The logical assumption is, therefore, that these pigments were formed by the liver itself directly from the excessive amounts of bilirubin derived from hemoglobin metabolism.

This experiment also afforded a rough estimate of the amount of blood destruction necessary to produce a given level of pigment values both in the blood-plasma and in the bile. Following an attack of hemolysis just sufficient to destroy about 800,000

red cells per cubic millimeter it takes about twenty hours for the bile pigments in the plasma and bile to return to their normal level.

A repetition of the above experiment confirmed the findings already described and substantiated the above conclusions.

The above case has been reported as an example of the means by which bile-pigment metabolism may be intelligently studied by means of the duodenal tube. The method outlined above has already been applied to a study of various pathologic conditions involving either directly or indirectly the biliary system. The results obtained in this field have already been extremely promising, but are beyond the scope of this present discussion. It is not the purpose of this paper to underestimate the value of a careful study of the cytology and bacteriology in a routine examination of the duodenal contents. The importance of the estimation of the bile pigments in the duodenal contents has been stressed at this time, however, in the hope that the renewed interest in duodenal analysis will result in additional observations upon that little understood function—the metabolism of the bile pigments.

CLINIC OF DR. HOWARD F. ROOT

NEW ENGLAND DEACONESS HOSPITAL

RARE PARALYSES IN DIABETES MELLITUS

AMONG the neurologic signs associated with diabetes mellitus paralyses, either of spinal or peripheral origin, have been regarded as rarities. The following 3 cases illustrate (1) multiple neuritis in diabetes complicated by chronic nephritis, and (2) peroneal paralysis in diabetes with arteriosclerosis:

CASE I

Miss H., aged thirty-six years, had a negative family and past history with the exceptions of measles and pertussis in childhood and the failure of the menses to appear.

On November 26, 1920 she first noticed polyuria and polydipsia. On January 15, 1921 her knees suddenly gave way and she fell to the ground. She arose unaided, but during the next few days rapidly lost strength in both arms and legs. She had severe pains in both extremities, which were considered to be "rheumatic." The loss of power during the first two or three weeks was progressive and she had been confined to bed since about January 20, 1921. She had no fever, cough, or sore throat.

She entered the New England Deaconess Hospital on April 28, 1921 for diabetic treatment.

Physical Examination.—Height, 61 inches; weight, 67 pounds (maximum weight, 85 pounds in 1910). Skin dry and pale, hair thin. Teeth showed some pyorrhea. Thyroid was not enlarged. Arteries were thickened. Ophthalmoscopic examination revealed slight pallor and edema of the retina, some

swelling of the optic disk, and marked tortuosity of the vessels. Blood-pressure was systolic 110, diastolic 70. The heart was not enlarged. A systolic murmur was heard at the apex. The abdomen was soft and the right kidney palpable, but not enlarged. Muscular weakness in both arms and legs was so extreme that the patient could not feed herself or raise a foot from the bed. The interossei of both hands, the glutei, and the muscles of the forearms and lower legs showed the most marked atrophy, but the muscles of the upper arms and thighs were soft and wasted. Soft pitting edema extended above the ankles, but was most marked on the dorsum of the foot.

Neurologic Examination.—Cranial nerves, pupils were equal and reacted to light and accommodation. A slight internal strabismus was noted, which the patient stated had been present since childhood. Palate was symmetric, speech and deglutition were normal. *Reflexes:* Biceps, triceps, radial, periosteal, and wrist reflexes were absent. Knee and Achilles' jerks were absent. Gordon, Oppenheim, and Babinski signs not present. Bladder and rectal sphincters were under normal control. *Sensation:* Both feet, especially on the plantar surfaces, were exquisitely sensitive to touch. Hands were not tender. Tenderness to deep pressure was present in the muscles of both calves. *Co-ordination and movement:* Bilateral toe-drop and wrist-drop were present, with a lesser degree of paresis in all the muscle groups of arms and legs.

Laboratory.—A single specimen of urine at admission contained 2.2 per cent. sugar, no diacetic acid, and no albumin. The specific gravity was 1016. The sediment contained no casts. Only 2 of 10 urine specimens examined contained albumin, and at no time were casts present in the sediment. Wassermann in the blood was negative. *Blood cytology:* 4,312,000 red corpuscles, 6500 white cells, stained smear showed slight variation in the size of red corpuscles, but no stippling. Hemoglobin 70 per cent. *Blood chemistry:* N. P. N. 60 mgm. per 100 c.c. Blood-sugar 0.4 per cent. Blood fat (Bloor) 1.38 per cent. CO_2 tension in the alveolar air 39 mm. Hg. Plasma chlorid 556, 571, and 586 mgm. per 100 c.c. *Renal function:* Phthalein

excretion was 27, 25, and 20 per cent. on three different occasions. Two-hour test, day amount 920 c.c., and night amount 1350 c.c. Specific gravity varied from 1009 to 1013. NaCl output was 8.1 gm.

Course in Hospital.—The urine became sugar free under dietetic treatment in three weeks, but the blood-sugar did not become permanently normal until the end of the fourth week. Return of muscle power began almost immediately and continued steadily during this time. On May 20th she could stand alone, feed herself, and dress herself. From this time on until her discharge on June 26th she gained steadily in strength, remaining constantly sugar free.

In spite of the improvement in the diabetes evidenced by the normal blood-sugar and normal blood fat, her renal function remained stationary. Non-protein nitrogen in the blood varied from 46 to 75 mgm. per 100 c.c. At discharge biceps, triceps, knee-jerks, and Achilles' reflexes were still absent, but the radial periosteal reflexes were obtained. Edema was absent, muscular power in arms and legs was nearly normal, and there was no tenderness in the feet or calves. A letter from her physician on March 10, 1922 states that she remained in good condition until within the last few weeks, when recurrent furuncles have proved a serious complication.

Diagnosis.—Four of the cardinal features of peripheral neuritis are presented in this case:

1. Paralysis, most marked distally and decreasing in degree as the trunk is approached.

2. Sensory changes. We have a history of pains in legs and forearms described as "rheumatic," and, on examination, tenderness, especially marked on the plantar surfaces of the feet, but also present in the calf muscles.

3. Atrophy. Atrophy of the interossei, glutei, and calf muscles was very marked, although even the muscles of the shoulders and the pectorals showed wasting.

4. Loss of deep reflexes. At the time of discharge the only reflexes which had returned were the radial periosteals.

Alcohol was ruled out with reasonable certainty.

Other possible causes to be considered are syphilis, acute ascending (Landry's) paralysis, and the polyneuritic form of anterior poliomyelitis. The immediate response to diabetic treatment suggests one element in the etiology. However, if this be considered coincidental, other diagnostic points may be brought forward. In the absence of an epidemic of poliomyelitis in the patient's home the sporadic form must be assumed. Pain is less common in this form, the patient had no fever, and the recovery without residual paralysis was remarkable considering the extent and duration of the paralysis when first seen. The absence of involvement of trunk muscles, of the muscles of deglutition and respiration, as well as the rapid recovery, serve to distinguish it from Landry's paralysis. The negative Wassermann and the absence of eye signs and sphincter disturbances are against syphilis. An interesting comparison may be drawn with the peripheral neuritis of beriberi. There, in addition to the neuritis, edema, and anemia, cardiac enlargement would be expected. However, the possible rôle of avitaminosis is suggested, and it is reasonable to consider the diet imposed on the patient before admission to the hospital. It included eggs, fresh vegetables, milk, and fruit, and therefore would lend little support to conjectures as to the rôle of avitaminosis in this instance, unless one assumed that the profound metabolic disturbance resulting from the combination of diabetes and chronic nephritis would impair the power of utilization of vitamins.

On the whole, the diagnosis of polyneuritis seems clear.

Etiology.—It is commonly stated that neurologic lesions in diabetes are more frequent and more severe when complicating such other conditions as syphilis, tuberculosis, and arteriosclerosis. This patient showed well-marked evidences of arteriosclerosis. Chronic nephritis with nitrogen retention may fairly be considered as a factor greatly complicating the metabolic disturbances due to diabetes. The question may well be raised as to whether nitrogen retention or a high sugar and fat content of the blood are more provocative of peripheral neuritis. Grube and other writers have commented on the fact that neuralgic pains in diabetes were often greatly lessened when hyperglycemia

disappeared. In Case I. marked improvement accompanied dietetic treatment, which reduced the blood-sugar to normal. Grube describes experiments of his own in which he produced neuritis by the injection of glucose in animals.

Dr. T. Murayama, in a personal communication, states that in severe beriberi fasting blood-sugar values of 0.23 per cent. are sometimes obtained without glycosuria. Improvement in the neuritis is often accompanied by a fall in the fasting blood-sugar. He has observed in severe cases of beriberi lowered carbohydrate tolerance with glucose tolerance curves of the diabetic type, which later changed to the normal type with improvement in the beriberi.

CASE II

Miss F., sixty-nine years, developed diabetes mellitus in December, 1920. Her father had also had diabetes. Six weeks before admission her left ankle suddenly gave way, and since that time she had fallen to the ground three times because of sudden turning of the ankle. Slight swelling was noticed at first, but no pain. She entered the New England Deaconess Hospital on January 22, 1922.

Physical Examination.—Arteriosclerosis was evident in the larger arteries and retinal vessels. The heart was slightly enlarged and a slight systolic murmur was heard at the apex. Blood-pressure was 163/74. The tendon reflexes of the arm were normal and the knee-jerks were present. Dr. E. W. Taylor found paralysis of the left peroneal nerve with resultant foot-drop, no disturbance of sensation, and considered the condition as due to diabetes. The urine contained 0.2 per cent. sugar, no albumin, and very rare casts. Wassermann in the blood was negative, blood-sugar was 0.22 per cent., and N. P. N. 36 mgm. per 100 c.c. Under dietetic treatment the blood-sugar fell to 0.12 per cent. and the urine became sugar free. The local treatment consisted of massage, electric stimulation, and a supporting brace.

At discharge on February 18th there was slight response to electric stimulation, but no response to voluntary effort.

CASE III

Mrs. A., aged fifty-five years, suffered repeated attacks of acute arthritis and tonsillitis before her twentieth year. She had six miscarriages due to nephritis, and albuminuria had been present ever since her first pregnancy. The onset of diabetes mellitus occurred in September, 1915, with polydipsia and pruritis. She entered the New England Deaconess Hospital March 13, 1922 for relief of epigastric distress.

Physical Examination.—Weight, 100 pounds; height, 5 feet, 5 inches. Pupils were equal and reacted to light and accommodation. Brachial arteries and retinal vessels showed moderate sclerosis. Blood-pressure 180/100. Liver and spleen were barely palpable. *Reflexes:* Biceps, triceps, and radial periosteal reflexes and knee-jerks were present. Achilles' reflex was not obtained. On the left a typical toe-drop without sensory disturbance was present.

Laboratory.—Blood Wassermann was negative. Urine: Specific gravity 1014, sugar 0, albumin slightest possible trace, blood 0, pus 0, casts 0. Phthalein excretion 54 per cent. in two hours, ten minutes. Two-hour renal test showed no fixation of gravity. *Blood:* Non-protein nitrogen 34.2 mgm. per 100 c.c., blood-sugar 0.17 per cent., plasma chlorid 605 mgm. per 100 c.c.

Treatment.—With dietary treatment the blood-sugar fell to 0.13 per cent. Electric treatment and a supporting brace were advised for the left foot. Gastric analysis and *x*-ray gave no evidence of disease of the stomach, intestines, or gall-bladder.

Cases II and III illustrate paralysis of a single peripheral nerve in the absence of the neurologic signs commonly found in diabetes, namely, absent knee-jerks and diminished sensation to light touch. Syphilis may be suspected in Case III, but we have a negative blood Wassermann, normal pupils, normal sphincter control, and normal reflexes.

DISCUSSION

Changes in the deep reflexes of the leg are doubtless the most common neurologic signs associated with diabetes mellitus.

Paresthesias and diminution of light touch sensation also occur frequently. Loss of tendon reflexes of the arm is much less common. Kraus found a diminution or absence of the deep reflexes in 30 per cent. of 450 cases of diabetes at the Vanderbilt Clinic. Williamson has called attention to the loss of vibratory sense in diabetes, and Kraus has stressed the diminished sensation to cotton wool.

The pathlogic studies of Williamson, Schweiger, and others have demonstrated the occurrence of degeneration of the intramedullary fibers of the posterior spinal roots, with resultant degeneration of the central continuations of their fibers in the posterior columns. These changes account for pseudotabes, areflexia, diminution of sensation, and paresthesias. Occasional instances of degeneration of the anterior horn cells have been reported, but, on the whole, there is surprisingly little evidence as to the nature of the changes in the central nervous system provoked by diabetes mellitus.

Clinicians have agreed in ascribing to diabetes a variety of neurologic lesions, yet there are few case histories of polyneuritis or of peripheral paralyses in the literature. Kraus found only one instance of polyneuritis in 700 cases of diabetes at the Vanderbilt Clinic, and that patient was also a chronic alcoholic. The patient described above is the only one in Joslin's series of more than 2000 diabetic patients. The peripheral paralyses are doubtless more common. The comparative infrequency of these conditions might suggest that no etiologic relationship to diabetes mellitus exists, but it is more likely that careful neurologic examinations would reveal a greater incidence of lesions of peripheral nerves than has heretofore been supposed.

SUMMARY

Three cases are reported illustrating:

(1) Polyneuritis occurring in the course of diabetes mellitus and chronic nephritis with nitrogen retention. Rapid subsidence of symptoms under diabetic treatment.

(2) Paralysis of the peroneal nerve in diabetes mellitus not associated with the more frequent areflexia and loss of sensation.

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CLINIC OF DR. THOMAS E. BUCKMAN

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TYPES OF PURPURA IN INFANTS AND CHILDREN

Definition and Types of Purpura. Group I. Purpura Due to Diminution in Number of Platelets in Circulating Blood: Idiopathic Purpura Hemorrhagica, Lymphatic Leukemia, Aplastic Anemia. Group II. Purpura Not Readily Explicable on Basis of Blood Findings: Symptomatic Purpura, Idiopathic Purpura.

GENTLEMEN: I shall present to you this morning 4 cases characterized symptomatically by the presence of purpura, that is, the apparently spontaneous extravasation of blood beneath the skin. In the first 3 of the cases we have at least a partial explanation of the mechanism by which the hemorrhages are brought about. In the last case we are unable to demonstrate in the blood any adequate cause for the condition; but I present this to you because it represents a clinical type which should be recognized as such until we are able to classify purpura on the basis of pathology or etiology.

Case I.—B. W., male, two years old. Family history and past history are not significant. He had always been well up to three months ago, when he was taken ill with scarlet fever. This was a moderately severe illness and at the height of the exanthem the appearance of many pinhead-sized purpuric spots over the abdomen and lower legs were noted. There was, however, no bleeding from a mucous membrane, and no ecchymoses were seen. Late in the course of the illness he developed a right-sided otitis media which necessitated paracentesis tympani, a discharge continuing up to one month ago. Six weeks ago a spontaneous hemorrhage from the right side

of his nose occurred. The bleeding continued for about two hours as a constant ooze, when it ceased, possibly due to packing with gauze soaked in 1 : 1000 epinephrin solution. Twenty-four hours later he showed numerous fresh pinhead-sized purpuric spots over the extensor surface of the forearms, lower legs, and abdomen, and a dollar-sized ecchymotic area appeared over the right shoulder. In the evening of the same day he again had a nosebleed from the same side of the nose. The oozing continued for several hours. A nose and throat consultant could find no cause in the nose to account for the epistaxis. Physical examination was negative except for the purpuric signs, which were as above described. T. 99.4, P. 120, R. 25. Urine negative. Stools negative; no macroscopic blood. Wassermann negative. Pirquet test negative. *x*-Ray of chest negative.

Blood: Bleeding time, two hours (normal, under three minutes).[1]

Coagulation time, fifteen minutes (normal, seven to twelve minutes).[2]

Clot very soft and not retracted at all after standing six hours at 37° C. No lysis.

Hbn. 55 per cent., R. B. C. 3,000,000 per cubic millimeter, W. B. C. 10,800.

Differential count: Polymorphonuclear neutrophils, 50 per cent.
Lymphocytes (all forms), 44 per cent.
Endothelial leukocytes, 3 per cent.
Myelocytes, 2 per cent.
Eosinophils, 1 per cent.

Tourniquet sign positive.

Examination of the stained specimen showed slight achromia of the red corpuscles, but no abnormality in size and shape, except for a few bottle- and flasked-shaped cells. There were no microcytes, fragmented cells, or tailed cells. Two normoblats were seen in counting 200 white cells. The percentage of reticulated cells was 5 per cent. No abortive leukocytes were seen.

There were 2 per cent. of adult myelocytes. Platelets were absent from the specimen examined. By count they numbered 22,000 per cubic millimeter.[3]

The patient was given a transfusion of 300 c.c. of whole blood by Dr. Kimpton. The bleeding from the nose immediately ceased. The bleeding time, which before transfusion had been two hours, was now only five minutes. There was no further bleeding from the mucous membranes, but, owing to the appearance of a crop of purpuric spots four days later, he was given a second transfusion of 300 c.c. There have been no bleeding, no purpuric eruptions, and no ecchymoses since then. Today the blood is entirely within normal limits:

Hbn., 75 per cent.
R. C., 4,000,000.
W. C., 8600.
Platelets, 360,000 per cubic millimeter.

The ear ceased to discharge two weeks following the transfusion. Since then the convalescence has been uneventful.

Discussion.—Epistaxis is a frequent event in older infants and young children. Rarely is it a manifestation of a disturbed coagulation mechanism. When persistent or especially when associated with bleeding from mucous membranes elsewhere or with purpuric spots or ecchymoses, grave suspicion should be entertained that the bleeding is due to some cause acting to reduce the number of platelets in the blood, and an examination of the blood should be made forthwith. The examination should be fairly complete and should embody the items above mentioned.

A STUDENT: Could this be a case of hemophilia?

DR. BUCKMAN: No. Purpura is not a symptom of hemophilia. Moreover, mucous membrane hemorrhages and ecchymoses appear in hemophilia, if at all, only after trauma and not spontaneously. Also, there is no family history of hemophilia among his brothers or maternal uncles. Hence from the history alone we feel rather inclined to exclude hemophilia. The blood examination proves that this is not hemophilia. In that condition the coagulation time is greatly prolonged, but the clot

when it does form is often well retracted. The bleeding time is not prolonged, and the platelets are either normal or increased in numbers, but deficient in quality.

A STUDENT: In what conditions is the number of platelets in the circulating blood decreased?

DR. BUCKMAN: In an infant of two years of age the following are the most frequently occurring conditions associated with a diminution in the number of platelets in the circulating blood: Idiopathic purpura hæmorrhagica (essential thrombopenia), acute lymphatic leukemia, aplastic anemia, and rarely certain infectious diseases, notably tuberculosis and diphtheria. In later life we should also include typhoid fever, pernicious anemia, myelogenous leukemia, industrial poisonings, notably benzene (benzol), and some tumor infiltrating the marrow. In this case there is no evidence that the patient has or has had diphtheria or tuberculosis. It is interesting to speculate what relation the scarlet fever bears to the diminution of platelets. It is possible that the toxin of this as well as of other infections might suppress the platelet-forming centers of the marrow. Of that we have no direct evidence. Nor does any considerable percentage of the cases of idiopathic purpura hæmorrhagica follow scarlet fever. On the other hand, many cases of idiopathic purpura hæmorrhagica give a history, as did this patient, of a hemorrhagic eruption during an attack of scarlet fever or measles. We seem to be dealing, then, with either aplastic anemia, lymphatic leukemia, or idiopathic purpura hæmorrhagica. On examining the blood findings one is impressed with the abundant evidence of marrow activity in so far as the leukocytes and erythrocytes are concerned in the face of a marked thrombopenia. The condition is, therefore, not aplastic anemia. The differential count, except for the presence of myelocytes, is entirely normal, and there is no enlargement of the peripheral lymph-nodes and the spleen is not palpable. We are, therefore, not dealing with a case of lymphatic leukemia. The history, physical examination, and blood findings are entirely consistent with a diagnosis of idiopathic purpura hæmorrhagica.

STUDENT: What is the rationale of transfusion therapy in this condition?

DR. BUCKMAN: It is supposed that the bleeding is due to a diminution in the absolute number of platelets. A transfusion of fresh, unmodified, normal blood supplies platelets in sufficient numbers to restore the normal process of coagulation of the blood. Since the life of the platelets is only from four to six days at the best, it often becomes necessary to repeat the transfusions at four- to five-day intervals. That was done once in this case. This disease is characterized by attacks of thrombopenia alternating with normal levels of platelets. In each case we hope to be able to supply platelets by transfusion until such a time as the marrow again takes up its function of forming platelets.

STUDENT: Why is it not possible to prepare suspensions of platelets and inject such a suspension instead of blood?

DR. BUCKMAN: Apparently the virtue of platelets lies in their being kept intact. Moreover, we are not sure that it is only platelets that a transfusion of blood furnishes. Apparently when platelets agglutinate they yield a substance which enables the blood to coagulate. Blood does not coagulate unless and until the platelets clump. After clumping the platelets are useless as an instrument for initiating coagulation. Other things being equal, the quality of the clot depends on the number of platelets that have agglutinated. Now the substance that the platelets yield is very unstable and rapidly becomes inert. Hence we cannot use an extract of platelets. Moreover, no one has yet devised a means of preventing the coagulation of platelets for longer than a very brief period of time. Hence we use fresh whole blood because it is the easiest way of supplying fresh unagglutinated platelets.

STUDENT: Are there any substitutes for platelets?

DR. BUCKMAN: There are certain proprietary substances which are alleged to accelerate the coagulation of blood when the delay is due to deficiency of platelets. Some investigators report favorably on the use of such preparations as "coagulose" and "kephalin." Any faith I have had in these has always led

to disappointment. I believe that they might be tried as a local application, not intravenously or subcutaneously, but that they should not be looked upon as a substitute for platelets (transfusion). It is true that fresh extract of tissues, notably lung tissue, have a remarkable effect in hastening the coagulation of purpuric blood. Presumably platelets are constantly yielding their thromboplastic material to the tissues, and this is being constantly utilized or destroyed and constantly replenished by the solution of further platelets. This accounts for the fact that the bleeding time is prolonged in purpura hæmorrhagica, but normal in hemophilia, whereas the coagulation time is prolonged in hemophilia, but normal or only slightly prolonged in purpura. The number of platelets in hemophilia is normal or increased. The difficulty seems to lie in the speed with which they go into solution and yield their thromboplastic substance. Yet the tissues are richly endowed with this substance in hemophilia. The bleeding time is found to be normal in hemophilia because a relatively small quantity of blood is mixed with a relatively large quantity of tissue juice. Hence also the absence of purpura in this disease. On the other hand, in determining the coagulation time, we have a relatively large quantity of blood mixed with a small number of platelets. Even though the platelets be normal in numbers, the blood will not clot until they agglutinate, which in hemophilia may be several hours. In idiopathic purpura hæmorrhagica the bleeding time is prolonged because the tissues are very poor in thromboplastic substance. The coagulation time may be normal because the platelets which are present will at once agglutinate, and these will be sufficient to permit of the formation of sufficient clot to prevent the escape of serum when one inverts the test-tube. On examination of the clot, however, it will be found to be very soft, loosely woven, and not retracted. Enough fibrin is formed in the normal length of time to simulate coagulation *in vitro*, but the quantity of fibrin formed is insufficient to prevent the oozing of blood *in vivo*.

STUDENT: How do you account for the presence of normoblasts and myelocytes in this patient's blood on the first examination?

DR. BUCKMAN: That is the reaction to hemorrhage. Normally the marrow reacts to a loss of about one-tenth or more of the blood volume by increased activity and by sending forth immature elements into the circulation. Hence after any brisk hemorrhage we find, normally, an increased number of platelets, a leukocytosis with a few myelocytes, and an increase in the number of immature red cells. The reaction is usually much more marked and more readily evoked, of course, in an infant than in an adult. In this case we see an attempt on the part of the marrow to react in the normal way. It has done the best it could. There are leukocytosis and myelocytes and also a number of normoblasts and other immature red cells. The thrombopenia is, of course, the outstanding feature of this blood.

STUDENT: What is the prognosis in this case?

DR. BUCKMAN: That is a difficult question to answer. This attack has been very mild. He is, of course, apt to have recurrences, any one of which may be fatal. The mortality statistics of the disease for different ages are so sparse that they do not help us much. We cannot say that the prognosis is better or worse under the circumstances than if he had developed his first attack in early adult life. The fact that this was a mild and easily controllable attack leads us to hope that future ones may be of a similar nature and that possibly they may disappear entirely. This, however, is mere speculation. The answer is that we do not know. If at any time in the future an operation becomes necessary, his blood should be examined, and even though normal, a donor should be at hand ready to be used if needed. Every attempt should be made to prevent bruising of the skin and mucous membranes. It would be a good thing if some member of the family of the same iso-agglutination group as this child were always within call so that no time would be lost if transfusion became imperative.

STUDENT: What is the etiology of the disease?

DR. BUCKMAN: At the present time the etiology of the clinical entity, idiopathic purpura hæmorrhagica, is entirely unknown.

Case II.—H. F. This patient is a girl three and a half years old. Both parents are living and well. There have been no other children. The family history is entirely negative. She herself has always been well and has seemed normal in every way until six months ago, when she had a fairly severe attack of measles. She recovered from this without any complications and has been well until the onset of the present illness, four weeks ago. At this time she had an acute respiratory disturbance characterized by coryza and dryness and soreness of the throat. She also complained at the time of some submaxillary tenderness on both sides. There seemed to be no fever. She was sick only for three days, and it was thought she had entirely recovered. One week later, however, her mother noticed the appearance of a crop of purpuric spots over the forehead. These disappeared in the course of a week, but ten days ago she was struck over the left shoulder by a falling broom. Over the left scapula region a palm-sized ecchymotic area at once appeared and has remained. The mother has commented on the disproportion between the lightness of the blow and the severity of the bruise. Three days ago an ecchymotic area the size of a dollar seemed spontaneously to appear over the right buttock, and yesterday another group of purpuric spots was observed over the right side of the forehead. The mother thinks she has become somewhat paler than usual during the past week and says that she is very listless and uninterested in her play. She complains of no pain anywhere. Her appetite has been very poor, but she drinks a great deal of water. There has been no bleeding from mucous membranes.

On physical examination we note a fairly well-developed, rather poorly nourished, but distinctly not emaciated, rather pale, and obviously sick little girl. T 100.6, P. 120, R. 28. Over the right side of the forehead there is a dollar-sized area made up of innumerable pinhead-sized hemorrhagic spots. Similar clusters of spots are seen over both shins and there are several individual hemorrhagic spots sparsely scattered over the abdomen and the left thigh anteriorly. The individual lesion is a macule and does not partake of the nature of an

urticarial wheal. Some of the individual lesions over the abdomen have a central portion which is darker than their brownish periphery. The abdominal purpuric lesions are somewhat larger than those seen elsewhere, but no one of them is larger than the head of a carpet tack. Over the left scapula is a palm-sized mottled area and a similar area is seen over the left buttock. The bones and joints are normal. Scalp and hair not remarkable. Eyes, ears, and nose normal. The teeth are in fair condition. The mucous membrane of the oral cavity is dry, but not red. The tonsils are very prominent, but not apparently the site of infection, and there is very little detritus in the crypts. There is no evidence of past or present oozing of blood from the mucous membrane of nose, mouth, or throat. The submaxillary glands are not enlarged on either side. There are three almond-sized glands in the left posterior cervical chain and a single pea-sized gland in the right posterior cervical chain. The glands in the left posterior cervical chain are hard and discrete. In both axillæ are walnut-sized masses of glands. A single bean-sized gland is felt in the subcutaneous tissue of the left arm on its postero-exterior surface about half-way from the shoulder to the elbow. The epitrochlears are not palpable. There are three almond-sized glands in the left groin, a single gland of similar size in the right groin, and two pea-sized glands in each popliteal space. The chest is normal. The level of the abdomen is that of the thorax. There is no spasm, tenderness, or rigidity. No evidence of free fluid. The lower edge of the liver is felt 2 cm. below the costal margin in the midclavicular line. The lower border of the spleen is felt 6 cm. below the costal margin in the midclavicular line. The right border of the spleen extends to the midline of the abdomen. No notch is felt. The spleen is fairly soft and not tender. There are no herniæ. Genitalia normal. Reflexes normal. No spasm and no paralysis. No edema anywhere.

Laboratory Findings.—The Wassermann tests of both parents' and patient's serum are negative. The Pirquet tuberculin test is negative. Roentgenogram of the chest shows a few slightly enlarged glands about the right hilus, but is otherwise

negative. The urine and stools are normal. The blood morphology is as follows:

Bleeding time, seven minutes.

Coagulation time, six and one-half minutes. Clot very soft and poorly retracted. No lysis.

Hbn. 35 per cent. R. B. C. 2,100,000 per cubic millimeter.

Platelets, 14,000 per cubic millimeter.

White corpuscles, 31,000 per cubic millimeter.

Differential count: Polymorphonuclear neutrophils, 11.5 per cent.
Endothelial leukocytes, 6 per cent.
Eosinophils, 1 per cent.
Myelocytes, 4.9 per cent.
Young lymphocytes, 8 per cent.
Mature lymphocytes, 30.2 per cent.
Old lymphocytes, 38.4 per cent.

Examination of the stained specimen shows the following: The prevailing size of the red cells is normal. There is no variation in size and shape and no achromia. Three erythroblasts were seen in counting 500 white corpuscles. The platelets are very markedly diminished. There are no abortive leukocytes, but there are 8 per cent. of very immature lymphocytes. These are large cells, larger than myelocytes, with a hyaline, grayish-blue, non-granular cytoplasm and a relatively small, dense, homogeneous, and deeply staining round nucleus. Some of these cells show "budding" in the cytoplasm periphery.

Discussion.—Let us consider first the clinical evidence, the history, and the physical examination. We cannot make a diagnosis on that alone, but we can limit the possibilities. We naturally think of acute lymphatic leukemia, idiopathic purpura hæmorrhagica, idiopathic purpura, tuberculosis, syphilis, and Hodgkin's disease. Tuberculosis and syphilis are rendered unlikely by the history and the absence of other signs of these diseases. The negative Pirquet and Wassermann tests help further to exclude these conditions. Idiopathic purpura frequently follows an acute pharyngitis or tonsillitis such as this child might have had four weeks ago. But generalized glandular

enlargement does not occur in this condition or in idiopathic purpura hæmorrhagica when either is present alone. Clinically, then, the case is one of acute lymphatic leukemia or acute Hodgkin's disease.

A STUDENT: Could this be glandular fever?

DR. BUCKMAN: Glandular fever and acute and subacute infections of the tonsils and sinuses might cause glandular enlargement, but such extensive purpuric manifestations are not seen in such conditions.

We must turn to the blood histology in order to make a diagnosis. A preponderance of lymphocytes, even over 70 per cent., and even with a total white count of 31,000 does not in itself signify lymphatic leukemia. It does, however, rule out Hodgkin's disease as far as it can be ruled out without a biopsy of a gland. It is the presence of the immature lymphocytes which makes us think that this must be lymphatic leukemia, and with this diagnosis all the data are entirely consistent.

A STUDENT: How do you account for the anemia and the purpura?

DR. BUCKMAN: Presumably the mechanism of the process is as follows: The lymphoid tissue hyperplasia infiltrates, so to speak, the bone-marrow, suppressing all the activities of the marrow. As a result we have a diminished output of platelets, red cells, and myelogenous leukocytes. The myelocytes which were seen are not an indication of increased marrow activity. They are frequently seen in lymphatic leukemia being pushed out, like the erythroblasts, from the marrow before they are mature. The anemia is thus of the myelophthisic variety and not due to increased blood destruction. This is further evidenced by the normal morphology of the red cells. As a result of the anemia we have the symptoms of weakness, listlessness, and loss of appetite. As a result of the paucity of platelets we have the purpura.

A STUDENT: At what level of platelets do purpuric manifestations occur?

DR. BUCKMAN: Generally speaking, we may expect purpuric manifestations when the platelets fall below 60,000 per

cubic millimeter. When they fall below 30,000 we expect spontaneous mucous membrane hemorrhages. It is remarkable that mucous membrane hemorrhages have not yet occurred in this case. They undoubtedly will occur very shortly. On the other hand, it must be borne in mind that sometimes purpuric lesions occur in lymphatic leukemia with a relatively high platelet count, and in this case the purpura is not due to the thrombopenia.

STUDENT: What is the treatment of the disease?

DR. BUCKMAN: There is no satisfactory treatment of acute lymphatic leukemia. In young individuals the disease runs an extremely rapid course and terminates fatally in six to ten weeks. Radiation, either *x*-ray or radium, which has a definite place in the treatment of the chronic type of the disease, might be tried, but will probably have no effect. Transfusion will temporarily arrest the purpura, but will not otherwise influence the disease. The treatment at present must consist chiefly of efforts to make the patient comfortable.

Case III.—The patient is too sick to be brought before the clinic. Hence I shall have to recite to you the history, physical examinations, and laboratory findings. The patient, J. J., is a girl eight years of age. The family history and past history are entirely negative. She was perfectly well three months ago. Shortly after this her mother noted that she was very pale, whereas formerly she had always had "rosy cheeks." A week later she complained of breathlessness and weakness, which together with the increasing pallor persisted. Two months ago a few purpuric spots were noticed over the shins. The next day a hemorrhage from the nose occurred and she was brought to the hospital. She had not seemed feverish, had not vomited, and had complained of no pain. The nasal hemorrhage had ceased when she reached the hospital. T. 102° F., P. 160, R. 30.

Physical examination at the time showed a very marked, white pallor. There were a few pinhead-sized purpuric lesions sparsely scattered over the lower legs and abdomen. In each axilla there were similar purpuric spots of a lighter color. Except

for these findings and the evidence of recent hemorrhage from the right side of the nose and an obviously rapid heart, the physical examination was entirely negative.

DR. BUCKMAN: From this story and physical examination what conditions would you think of?

A STUDENT: Aplastic anemia and lymphatic leukemia.

DR. BUCKMAN: Yes. And I should add acute endocarditis, Streptococcus hemolyticus septicemia, and perhaps typhoid fever. We cannot make an absolute diagnosis without further evidence. The urine and stools were negative. Blood examination showed the following:

Hemoglobin, 20 per cent. R. B. C., 600,000 per cubic millimeter.

Reticulated R. B. C., 0.1 per cent.[4]

White cell count, 3800 per cubic millimeter.

Differential count: Polymorphonuclear neutrophils, 32 per cent.
Eosinophils, 1 per cent.
Endothelial leukocytes, 3 per cent.
Lymphocytes, 64 per cent.

Examination of a stained specimen revealed the following: The morphology of the red cells was normal and there was no achromia. No microcytes and no fragmented cells were seen. The average size of the cells was normal. There were no abortive or immature leukocytes seen. Platelets were exceedingly rare.

Coagulation time, twelve minutes. Clot very soft and not retracted after six hours of incubation. No lysis.

Bleeding time, eighteen minutes.

Fragility test, hemolysis begins at 0.35 per cent. sodium chlorid concentration and is complete at 0.30 per cent. (Normal control hemolysis begins at 0.40 per cent. sodium chlorid concentration and is complete at 0.30 per cent.)

This blood-picture is very characteristic. Evidently a cessation of activity of all the myelogenous elements has occurred, leaving only the lymphocytes in their normal numbers. Note that the morphology of the red cells is normal in spite of a very severe degree of anemia.

The results of the fragility test are very interesting. This test is performed by setting up a series of about 20 small test-tubes, to each of which is then added 1 c.c. of hypotonic sodium chlorid solution in diminishing concentration from 0.60 to 0.20 per cent. In each successive tube the concentration of sodium chlorid is 0.02 per cent. less than in the tube immediately preceding it. To each tube is now added 0.1 c.c. of washed red cells. The tubes are shaken and allowed to stand four hours in the ice-chest. At the end of this time the concentration of sodium chlorid in the tube in which the first tinge of pink is seen is noted and likewise the concentration of sodium chlorid in the tube in which hemolysis is first observed to be complete. This latter end point may be determined colorimetrically by comparing the color in the tubes in the rack with the color imparted to a solution of red cells made by adding 0.1 c.c. of cells to 1 c.c. of distilled water in a precisely similar tube. Normally the values for these two limits are 0.40 and 0.30 per cent. respectively, the span being about 0.10 per cent. In some conditions, such as hemolytic jaundice, hemolysis may begin at a much higher concentration of salt, increased fragility, and the length of the span may also be increased. In this case there is a slightly diminished fragility and a definitely diminished length of span, only 0.06 per cent. This presumably means that the cells approach one another in their properties and is evidence of aplasia.

A further test was done in this case in our attempts to determine whether the anemia was of myelophthisic or of hemolytic nature. This is a sort of fragility test in which blood-serum of known concentration besides salt solution is used. I devised this test two years ago, and since that time Dr. Horrall and I believe we have collected sufficient data to establish its value.

The results of the test in the case of this patient are shown in the chart. The vertical columns, as indicated by the legend, refer to the different solutions in which the cells were suspended, hypotonic sodium chlorid solution, hypotonic patient's serum, and hypotonic normal serum of the same iso-agglutination group as the patient's serum. In each case the concentration of the

solution in the tube in which hemolysis was observed to begin and in the tube in which hemolysis was observed to be complete were determined cryoscopically and the results translated

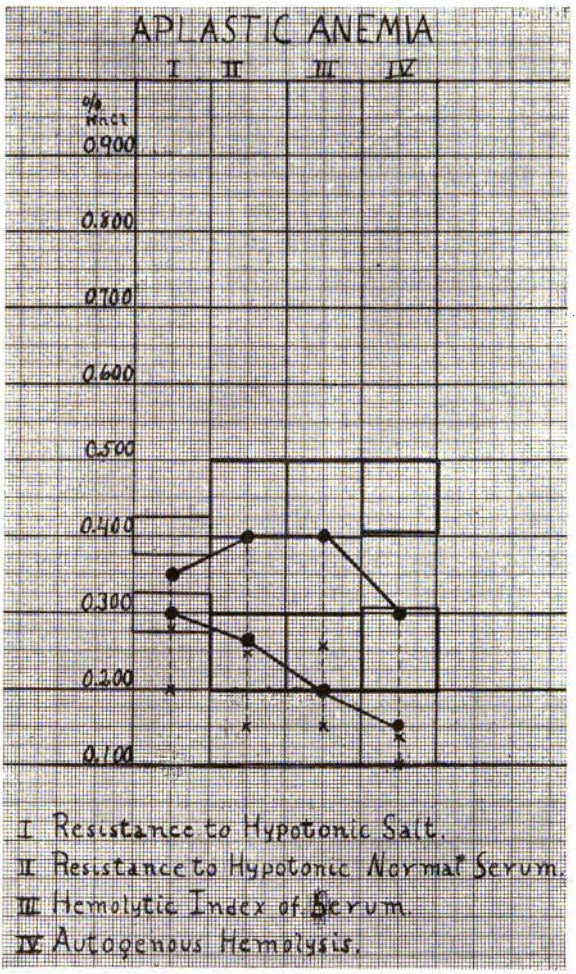

Fig. 277.

into equivalent concentrations of sodium chlorid, the ordinates. The spaces enclosed by the heavy lines indicate the limits of resistance of normal cells both to beginning and complete hemolysis when they are placed in salt solution, in hypotonic normal

serum, and in their own serum, autogenous hemolysis. The solid blue lines indicate the behavior of the cells and serum in this particular case. The dotted vertical lines indicate the maximal and minimal normal spans of hemolysis in salt solution and in serum. Hence in Column I we have a comparison of the cells of this patient with normal cells with respect to their deportment toward hypotonic sodium chlorid solution. The cells are thus seen to be distinctly less fragile than normal and also to exhibit a shorter span than the minimal span of normal cells in salt solution. In Column II we have a comparison of the patient's cells with normal cells as regards their behavior toward hypotonic normal serum. Except for a slightly shortened span there is no abnormality revealed here. In the third column the influence of the patient's serum on normal cells of the same isohemolytic group is compared with the influence of the serum of a normal individual on the cells of another normal individual of the same isohemolytic group. That is, Column III measures the hemolytic activity of the serum. In this case it is within normal limits. In Column IV the behavior of the patient's cells toward the patient's own serum is compared with the behavior of the cells of a normal individual toward that individual's own serum. In this case there is a markedly diminished fragility of the patient's cells toward her own serum. So far as this test is concerned, we may summarize the situation with respect to this individual case by saying that the red corpuscles show a slightly diminished fragility toward hypotonic salt solution and a greatly shortened span in salt solution. With respect to the influence of the patient's serum on the patient's cells there is evidence of a sparing action, whereas the patient's serum does not behave abnormally toward normal cells. In other words, the patient's serum is not hemolytic. The patient's red corpuscles are distinctly less fragile than usual in their own serum and are presumably approaching the same age as indicated by the short span. In anemia due to hemorrhage we get the same picture except that the span is not shortened. The mechanism seems to be then as follows: As a result of the anemia a compensatory sparing action is developed by the

serum toward its own cells. As a result of the aplasia, cells that remain in the circulating blood are approaching more and more the same age, and hence we get a short span. In anemias in which intravascular hemolysis occurs, pernicious anemia, Streptococcus hemolyticus septicemia, lead-poisoning, we get the opposite: a longer than normal span and an increased fragility of cells toward their own serum.

The marrow in this case is surely aplastic. The question arises, What is the cause of the aplasia? Lymphatic leukemia might produce such a picture. But a leukopenia without any abnormal lymphocytes and without any glandular enlargement is a rare finding in a case of lymphatic leukemia which has not been treated by radiation. It is conceivable that typhoid fever might produce this picture. Blood for culture was taken on admission and on two successive occasions. All specimens were negative. Three Widal tests and two cultures of the stools were negative. Besides, there have been no signs of typhoid fever—palpable spleen, roseola, etc., and the clinical course has not simulated typhoid fever in any way. Streptococcus hemolyticus septicemia might cause a severe anemia and terminally a leukopenia and a thrombopenia. But in such a case the anemia would almost surely be of the hemolytic type. We should expect to see variations in the size and shape of the red cells with microcytes, fragmented cells, and tailed cells appearing. We should expect the cells to be very much more fragile than normal toward their own serum rather than less fragile as they are. Also we would expect an increase rather than a diminution in the number of reticulated cells. The normal number is about 1 per cent. or under. In this patient there are only about one-tenth as many. These cells are presumably young cells and an increase in their numbers usually signifies increased marrow activity. Moreover, three blood-cultures were negative and there is no evidence of a focal infection anywhere in this patient.

Subacute and acute endocarditis are frequently associated with a severe anemia and often with purpura. In such cases, however, there is usually no diminution in the number of plate-

lets, and a leukocytosis rather than a leukopenia is the rule. In endocarditis the purpura is probably never due to thrombopenia. It is probably the result of local vascular changes or the result of emboli. In the latter case the individual lesions often show a dark central area surrounded by a lighter border. In this particular case the rapid pulse and the fever are the only other features that suggest endocarditis. It cannot be positively ruled out, but if it is present there must be some other condition also present to cause the aplasia.

There are two possibilities: A tumor infiltrating the marrow and some toxic substance (benzene). Tumor of the marrow cannot be excluded. It does occur. We have no knowledge that this child had access to benzene. Still there might have been some other substance which was causing the aplasia. When we cannot find a cause for aplasia we make a diagnosis of primary aplastic anemia. Such was and still is the diagnosis on this case.

STUDENT: Could this be a terminal phase of pernicious anemia?

DR. BUCKMAN: Theoretically, yes; practically, exceedingly unlikely, and for the following reasons: Pernicious anemia is exceedingly rare at the age of eight years. Gastric contents analysis has been performed twice in this case, and in both instances free hydrochloric acid has been found. Free hydrochloric acid almost never occurs in pernicious anemia, although some individuals without free hydrochloric acid in their stomach contents certainly do not have pernicious anemia. Moreover, the anemia is distinctly not of a hemolytic type. Finally, the clinical course of pernicious anemia is wanting in this case. The absence of neurologic signs and symptoms and the absence of previous gastro-intestinal symptoms do not rule out pernicious anemia. They may be absent in any case, and the neurologic findings are especially prone to manifest themselves only in adults. I think we must rest then with a diagnosis of primary aplastic anemia. The aplasia evidently began something over a month before she entered the hospital. The first symptoms were those of anemia—pallor, breathlessness, fatigue, anorexia,

followed later by tachycardia. Then followed the purpura as the platelets became involved and, finally, the nasal hemorrhage. The leukopenia, of course, gave rise to no symptoms.

The natural course of this disease is progressively downward to a fatal termination in from five to eight weeks after the first symptoms are observed. There is no known agent which will retard the progress of the disease. However, in the hope that the toxic substance causing the aplasia might cease to act or be neutralized or be eliminated we have continued to advise transfusion. In the past seven weeks Dr. Kimpton has given to this patient nine infusions of whole blood. Her blood-picture is essentially the same now as at entrance except that she is much less anemic. Her red cell count this morning is 3,100,000 and she is distinctly less dyspneic than at entrance. She has to be transfused every five or six days. Otherwise she would bleed to death. In other words, it is the life of the platelets (four to six days) that controls the frequency of the transfusions. The life of the red cell is probably at least thirty days, and hence these cells accumulate.

The outlook for this little girl is almost certainly unfavorable. Rarely a recovery following many transfusions has been reported. Transfusion merely tides the patient over for a few days. Yet there is no other treatment. Whole blood is preferable to citrated blood in this condition because we wish to introduce as many platelets as possible.

These 3 cases, idiopathic purpura hæmorrhagica, acute lymphatic leukemia, and aplastic anemia, illustrate the most frequent types of purpura due to a diminished number of platelets seen in infants and children. These diseases also are the commonest causes of pathologic mucous membrane hemorrhages in infants and children, and should always be suspected when either of these signs is present and particularly if both are present.[5]

Purpura, however, with or without mucous membrane hemorrhage, frequently occurs in infants and children without there being any demonstrable abnormality in the histology of the blood. Such a case is the following:

Case IV.—H. Y. G. This is a boy seven years of age. Both parents are living and well and there is no family history of hemophilia, purpura, tuberculosis, syphilis, or other disease that has any bearing on the present condition. There is one other younger child living and well. The patient had measles at two years, whooping-cough at five years, and scarlet fever a year ago. From each of these he recovered apparently completely and except for these illnesses he has always been well. Three days ago he awakened in the early morning with a severe pain in the region of the umbilicus. The pain made him cry out, but the mother says he could not localize it very well. Shortly afterward he vomited a small amount of greenish material. This seemed to relieve the pain somewhat, but he continued to complain of abdominal discomfort until he was brought to the hospital the morning of the same day. Before coming to the hospital he had one stool about which the mother noticed nothing unusual. On admission he appeared as a well-nourished and well-developed boy moderately sick, but not apparently in pain. T. 101° F., P. 120, R. 25. The bones and joints were normal. Scalp and hair clean. There was no glandular enlargement. The skin showed no eruption of any kind. The examination of the eyes, ears, nose, and throat revealed no abnormality. The chest was resonant throughout, the breathing normal, and there were no râles. The heart was normal. There was much voluntary spasm of the abdomen, but no definite localized spasm or tenderness. Liver and spleen not felt. No herniæ. Genitalia normal. No spasm or paralysis of the extremities. Reflexes equal and normal. No edema. The urine was normal. The blood showed the following:

Hbn. 80 per cent.; R. B. C. 4,000,000; W. B. C. 8000.

Differential count within normal limits.

A surgical consultant thought there was no operable condition in the abdomen. During the afternoon he passed a very dark stool in which occult blood was demonstrable. He improved markedly during the evening, but again complained of pain in the abdomen yesterday morning. At this time there were noticed for the first time several purpuric spots over the

abdomen and two quarter-sized hemorrhagic blebs over the right tibia. These lesions, but no new ones, are still present, as you see. A second examination of the blood was made yesterday afternoon and revealed the following:

Hbn. 78 per cent.; R. B. C. 4,000,000; W. B. C. 8800.

Differential count: Polymorphonuclear neutrophils, 68 per cent.
Eosinophils, 1 per cent.
Endothelial leukocytes, 6 per cent.
Lymphocytes, 25 per cent.

Examination of a stained film showed the red cells normal in every respect. There were no abortive or immature leukocytes. The platelets appeared abundant in numbers.

Platelet count, 340,000.

Bleeding time, two and a half minutes.

Coagulation time, thirty minutes. Clot poorly retracted after six hours of incubation. No lysis.

Further laboratory data: Roentgenogram of chest negative.

Pirquet test, negative.

Today he seems very much better (T. 98° F., P. 90, R. 24).

Discussion.—This is a case in which we have both purpura and mucous membrane hemorrhages and, except for the prolonged coagulation time and rather poorly formed clot, a normal blood. It is obvious that the purpura and mucous membrane hemorrhage are not caused by any of the factors which were operative in any of the previous cases that I have shown you. The most important question to decide now is whether the purpura is a manifestation of some underlying disease or whether it in itself is a disease entity. That is, is this symptomatic purpura or idiopathic purpura, or is this a case of that rare condition, purpura fulminans. The commonest diseases in which purpura is a symptom are epidemic meningitis, typhoid and typhus fever, syphilis, tuberculosis, endocarditis, and certain chronic non-infectious diseases, especially chronic nephritis. Drugs, especially iodids, bromids, atropin, salicylates, and mercury may also cause a purpuric eruption. There is no evidence that he has any of these diseases above mentioned, and

so far as can be determined he has not been taking any drugs whatever. It is doubtful, then, if the purpura in this case is a manifestation of some underlying disease. Moreover, the fact that he is getting better proves that this is not purpura fulminans. We are left, then, with idiopathic purpura, albeit with hemorrhages, as the most likely diagnosis in this case. Idiopathic purpura may manifest itself simply as purpura, without any other symptoms. It may take the form of a hemorrhagic urticarial eruption or of an erythema. Often when of the latter type there is a history of previous tonsillitis, Schoenlein's peliosis. The purpura may coexist with arthralgia, rheumatic purpura; or with visceral lesions, especially hemorrhages from the intestinal mucosa, as it did in this case, when the condition is usually spoken of as Henoch's purpura.

A STUDENT: What is the significance of the prolonged coagulation time?

DR. BUCKMAN: I do not know. It is commonly said that no demonstrable alteration in the coagulation mechanism exists in idiopathic purpura and that the extravasation of blood is probably due to changes in the vessel walls. I have noticed a slightly but definitely prolonged coagulation in several cases of idiopathic purpura. I think this may indicate that the condition is a form of allergy, although the study of these cases by the cutaneous application of proteins has been disappointing.

A STUDENT: What is the prognosis?

DR. BUCKMAN: Excellent. He may have further attacks. These may be more severe and last longer than the present one, but the chances for recovery from any given attack are good.

There is no satisfactory treatment of the disease. The tests for protein sensitization might be tried. It is probable, however, that more information will be yielded by a study of the serum precipitins in these cases than by the cutaneous reactions. It would be difficult to determine the value of withholding certain proteins from the food except in cases where the attacks are very frequent, inasmuch as the disease tends to disappear spontaneously with advancing age.

The types of purpura which I have demonstrated this morn-

ing may, of course, occur at any age. Certainly this is true of idiopathic purpura hæmorrhagica. Nevertheless, aplastic anemia, acute lymphatic leukemia, and idiopathic purpura are seen more commonly in children than in adults, and together with hemorrhagic disease of the newborn and hemophilia they constitute the principal causes of pathologic hemorrhage in early life.

In conclusion, let me recommend to you certain original articles for the further elucidation of the subject of purpura:

1. Minot, G. R.: Studies on a Case of Idiopathic Purpura Hæmorrhagica, Amer. Jour. Med. Sci., 152, 48, 1916.
2. Lee, R. I., Vincent, B.: The Coagulation of Normal Human Blood, Arch. Int. Med., vol. 13, p. 398, 1914.
3. Buckman, T. E., Hallisey, J. E.: Studies in the Properties of Blood-platelets, Jour. Amer. Med. Assoc., vol. 76, p. 427, February 12, 1921.
4. Cunningham, T. D.: A Method for the Permanent Staining of Reticulated Red Cells, Arch. Int. Med., vol. 26, p. 405, 1920.
5. Minot, G. R.: Diminished Blood-platelets and Marrow Insufficiency, Arch. Int. Med., vol. 19, p. 1062, 1917.

CLINIC OF DR. W. RICHARD OHLER

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LESSONS TO BE LEARNED FROM REPEATED GLUCOSE TOLERANCE TESTS

DURING recent years numerous articles have appeared in the literature dealing with the subject of glucose tolerance tests in various types of disease. Prominent among the disease conditions so studied have been hyperthyroidism, chronic arthritis, hypertension, carcinoma, ulcer of the stomach or duodenum, obesity, and diabetes. Certain observers have gone so far as to claim that variations in the reaction of the individual to a glucose test-meal are of distinct diagnostic import. Such claims have been made especially for chronic arthritis and for stomach ulcer or carcinoma. In fact, so many claims have been made for the test and so many variations in reactions have been reported that one is forced to conclude that sugar tolerance studies are either of tremendous but unappreciated value or of no value at all. It is not the purpose of this paper to review the work done on sugar tolerance tests or to attempt any standardization of the test,[1] regardless of the fact that such a standardization of values is necessary, but merely to raise the question of the practical value of such tests in the study of a given condition, that of doubtful or mild diabetes.

Ordinarily, the diagnosis of diabetes mellitus is a simple matter, but in any large hospital clinic cases are constantly

[1] In a paper not yet published Horace Gray, of Boston, has made an extensive review of 900 sugar tolerance tests in the literature, with particular reference to the range of normal reactions and to the various types of test-meals in use.

found where the diagnosis is doubtful. In general, these cases may be divided into two groups:

(1) Cases of persistent glycosuria regardless of the diet.

(2) Cases of only occasional glycosuria.

Of course, it is well known that there are certain types of disease conditions other than diabetes where sugar sometimes appears in the urine and where the reaction to a glucose meal may be abnormal. Prominent among such conditions are nephritis, hypertension, arteriosclerosis, chronic arthritis, carcinoma, cirrhosis of liver, gall-bladder disease, head injuries, injuries to the long bones, and endocrin disturbances, particularly of the thyroid, adrenal, and pituitary glands. The cases presented in this paper, however, are cases in which the only clinical evidence of diabetes has been glycosuria and where there have been no complicating conditions.

For many years glucose tolerance tests of one kind or another have been in more or less common usage. It is, however, only during recent years that the study of the blood-sugar has been taken into consideration. For example, it is a common practice among insurance companies to give a doubtful case of diabetes 100 grams of glucose and then to test the urine for sugar at, say, a two-hour interval following the injestion of the glucose. It has been shown, however, by many observers that this practice is not sufficiently accurate because it does not take into consideration the blood-sugar content. Furthermore, there have been various types of test-meals, in more or less common usage, as a means of determining sugar tolerance. Probably the most common type is the one mentioned above, that of giving 100 grams of glucose.

Recently Janney and Isaacson[1] have suggested a tolerance test which consists of the following technic:

(1) Patient is given 1.5 grams of glucose per kilogram of body weight. This glucose is dissolved in water of an amount equivalent to 3 c.c. of water per gram of glucose. The resulting solution is flavored with either lemon- or orange-juice.

(2) The patient voids before the solution is given and again

[1] References, Jour. Amer. Med. Assoc., 1918, vol. 70, p. 1131.

two hours after the solution is given (a collection of urine at the end of one hour as well as at the end of two hours is probably more advisable).

(3) Blood-sugar determinations are made at the beginning of the test period and at the end of forty-five minutes or one hour and at the end of the two-hour period.

(4) The test is begun following a twelve-hour fasting period and the patient receives nothing to eat or drink during the time of the test.

During the past three years some 400 tolerance tests have been done at the Boston City Hospital according to the technic described above. No claim is made that this particular tolerance test is the most advisable and, as a matter of fact, it is doubtful if anyone can make such a claim for any sugar tolerance test at present in use. Our chief reason for using the above-mentioned test is that the studies were begun with this test, and it has been our desire to continue our observations without changing the technic of the test.

Just as there is a doubt as to the proper kind of sugar tolerance test, so there is considerable doubt as to what constitutes the normal reaction to a glucose meal. For example, if a normal individual is given a glucose meal such that he is getting 1.5 grams of glucose per kilogram of body weight, the reaction as studied by both the urine and the blood-sugar may vary considerably. Table I represents a study of 8 normal young persons. It will be noted that the blood-sugars at the end of the first hour show a moderate rise and that the blood-sugars at the end of the second hour come down to within one or two points of the fasting figure, or even below the fasting figure. It will also be noted that in no case was sugar found in the urine.

However, in the study of normal cases other observers have noted that the blood-sugar at the end of the first hour sometimes shows a very sharp rise, going as high as 0.17 per cent. or even higher, and that at times the blood-sugar at the end of the second hour does not return to within one or two points of the fasting figure. Furthermore, it has been noted that at times normal individuals excrete small amounts of sugar in the urine

following such a test. It would seem, therefore, that there might be considerable doubt as to what is normal and what is abnormal following a glucose meal. We are at once, then, confronted with the fact that there is a considerable variation in the type of test-meal used, and that there is often considerable doubt concerning the normal reaction.

In addition, we are also confronted with the question as to whether or not a glucose meal does permanent harm. It is conceivable that in a case where the pancreatic function is near or at the breaking point, an unusual load of glucose might do permanent harm. All of these things must be borne in mind in attempting to find any practical application for glucose tolerance tests. But it is probably fair to say that if glucose tolerance tests have any practical value at all, the tests should be of service in the study of the types of cases presented in this paper.

The following is a record of a few of the cases which have been under observation at the Boston City Hospital:

NORMALS

Case Numbers	1	2	3	4	5	6	7	8
	Percentages							
Fasting blood-sugar	0.07	0.08	0.076	0.08	0.07	0.098	0.09	0.065
Blood-sugar one hour after glucose meal	0.09	0.085	0.08	0.09	0.08	0.11	0.085	0.09
Blood-sugar two hours after glucose meal	0.08	0.076	0.07	0.08	0.065	0.10	0.085	0.08
Glycosuria	0	0	0	0	0	0	0	0

Group I: *Case I.*—A. F. L., age forty. Patient gives a history of having shown sugar in the urine for a period of ten years following an attack of scarlet fever. During this period he has had practically none of the classical symptoms of diabetes with the exception of some weakness and considerable nervousness and irritability. He has been under treatment more or less of the time, going from one physician to another, but, despite rigid dietary measures, states that he has never been sugar free. He feels that a good deal of his weakness and nervousness has been due to the methods of treatment rather than to the disease itself.

When first seen in May, 1921 his fasting blood-sugar was 0.06 per cent. He remained in the hospital for ten days, during which time his urine constantly showed from 0.2 to 0.8 per cent.

of sugar despite the fact that he was on a rigid diet and had a starvation period of two days. At the time of discharge his fasting blood-sugar was 0.07 per cent., and a blood-sugar taken two hours after a fairly liberal meal was also 0.07 per cent.

The record of his glucose tolerance tests is as follows:

	June, 1921. Per cent.	February, 1922. Per cent.
Fasting blood-sugar	0.07	0.076
Blood-sugar one hour after glucose meal	0.13	0.07
Blood-sugar two hours after glucose meal	0.064	0.076
Urine before test	0.9	Trace
Urine after test	0.7	Trace
Weight	129 pounds	143 pounds

Comment: This patient has never had an increase in blood-sugar and since May, 1921 his tolerance tests have remained normal despite definite increase in weight. Clinically, he feels better than at any time during the past ten years largely because the dread of diabetes has been removed. Personally, I feel that this patient must at present be classed as a case of renal glycosuria, and I think it is perfectly safe to allow him to remain on an unrestricted diet.

Case II.—J. B., age thirteen. Patient reported at the Out-patient Department in April, 1920 because of enuresis. Sugar was found in the urine at this time and patient was admitted to the hospital for treatment. He remained in the hospital for two weeks, during which time the amount of sugar in the urine varied from a trace to 0.5 per cent. apparently regardless of changes in the diet. The highest amount of carbohydrate in the diet for any one day during this period was 120 grams. His fasting blood-sugar, which was done on several occasions, was never higher than 0.08 per cent.

Since leaving the hospital the patient has been seen occasionally in the Out-patient Department up to the present time. The urine has always contained small amounts of sugar despite the fact that the patient has never adhered to any dietary restrictions and has eaten about as he pleased, including the usual amount of candy and pastry. Also during this period the patient has gained in height and weight and apparently has been per-

fectly normal in every respect. Furthermore, repeated fasting blood-sugar determinations have been within normal limits.

The record of this patient's glucose tolerance tests is as follows:

	May, 1920. Per cent.	Aug., 1921. Per cent.	Feb., 1922. Per cent.
Fasting blood-sugar	0.07	0.06	0.07
Blood-sugar one hour after glucose	0.10	0.07	0.08
Blood-sugar two hours after glucose	0.06	0.07	0.066
Urine before glucose meal	0.6	0.7	0.3
Urine after glucose meal	....	0.8	0.3
Weight	....	98 pounds	107 pounds

Comment: Glucose tolerance tests perfectly normal since May, 1920, despite the fact that patient continues to show sugar in the urine. Patient has grown normally, and to all intents and purposes behaves and acts like a normal boy. I feel that at present this patient must also be classed as a case of renal glycosuria.

Summary of Group I.—The above 2 cases have been selected as examples of cases which fall in Group I, mentioned above. The problem of so-called renal glycosuria is always interesting, for one constantly wonders whether renal glycosuria is a distinct clinical entity or whether it represents a stage in the development of true diabetes. Certainly the question cannot be answered until patients have been under observation for a long period of time. The diagnosis of renal glycosuria should be made with great caution, and patients should be impressed with the importance of keeping themselves under careful supervision, including supervision of weight, because it is probably important not to allow such patients to exceed their normal weight. Assuming that such careful supervision is maintained, there seems to be no harm in allowing these cases to remain on a diet unrestricted except for sugar and candy. As a matter of fact, such patients feel better and clinically are better than during the attempts to get them sugar free. To my mind they represent one of the most important groups of diabetics and a class of patients for which the physician can perform a real service.

Group II: *Case I.*—Dr. H., age twenty-seven. Patient con-

sidered himself perfectly well until January, 1921, when he applied for life insurance, and was told that there was a small amount of sugar in the urine. To the best of his knowledge sugar had never been discovered in the urine before, even though it had been his habit to have occasional urinary examinations. Following the discovery of sugar in the urine the patient was kept on an unrestricted diet for three days, and each specimen of urine passed was examined for sugar. No sugar was found during this three-day period in any specimen. The fasting blood-sugar done on two separate occasions was 0.08 per cent.

The record of his glucose tolerance test is as follows:

	May, 1921. Per cent.
Fasting blood-sugar	0.08
Blood-sugar one hour after glucose meal	0.21
Blood-sugar two hours after glucose meal	0.155
Urine two hours after glucose meal	0
Weight	164 pounds

Comment: This type of reaction is not uncommon. It will be noted that the blood-sugar at the end of the first hour rises above 0.16 per cent. (often claimed as the renal threshold figure for sugar), and that the blood-sugar reading at the end of the second hour does not fall to within one or two points of the fasting figure. If we accept certain described standards for glucose tolerance tests, then this test should be classed as abnormal and should be interpreted as showing a distinct lowering of the tolerance for sugar. However, it is probably safe to say that if we call all such cases diabetes, then there are probably a great many more diabetics in the country than we have previously thought. Furthermore, this patient has never shown sugar in the urine since the occasion mentioned above, although the urine has been tested each month since May, 1921.

It is my feeling that this patient is probably not a diabetic, but the question can only be determined by succeeding tests over a period of years. In view of his tolerance test, he should be careful not to become overweight and he should omit sweets from his diet.

Case II.—T. H., age sixty-four. Admitted to the hospital in October, 1920 with a diagnosis of hemorrhoids. Sugar was found in the urine on one occasion during his stay of three weeks in the hospital. The fasting blood-sugar at this time was 0.08 per cent. Since November, 1920 patient has been seen in the Out-patient Department at intervals of about three months, and on a very few occasions a slight trace of sugar has been found in the urine. During this time the patient has been on an unrestricted diet, but since January, 1921 he has been using no sugar and no pastry.

The record of his glucose tolerance tests is as follows:

	January, 1921. Per cent.	July, 1921. Per cent.	February, 1922. Per cent.
Fasting blood-sugar	0.118	0.08	0.104
Blood-sugar one hour after glucose	0.23	0.25	0.217
Blood-sugar two hours after glucose	0.247	0.18	0.149
Urine one hour after glucose meal	....	....	0
Urine two hours after glucose meal	0.23	Trace	Trace
Weight	165 pounds	172 pounds	173 pounds

Comment: Note that in January, 1921 the patient's glucose tolerance test gave a result like that of a true diabetic despite the fact that at this time sugar was found in the urine only occasionally. The patient was told that he was a diabetic and was impressed with the importance of cutting down the sugar content of his diet. It is interesting to note that the restriction of the diet, even though moderate, has apparently been sufficient to improve his tolerance as is shown by the subsequent tests in July, 1921 and February, 1922. This improvement has taken place despite the fact that patient has gained slightly in weight. In my mind this is a very important case and probably exemplifies what can be done in the management of a mild diabetic. It is not too much to hope that as time goes on this patient's tolerance for sugar may return to normal. If such is the case he might be termed by an observer who did not know his complete history a cured diabetic. As a matter of fact, such cases are not cured, but are, strictly speaking, "arrested" cases of diabetes. There is probably no limit to the duration of this

arrested period, providing the patient does not overburden the organism with sugar.

Case III.—T. McC., age thirty-nine. Patient was admitted to the hospital in January, 1920 for acute back strain. He remained in the hospital for two weeks and small amounts of sugar were found in the urine on three occasions during this period. Since then the patient has been seen at intervals of six months in the Out-patient Department and urine samples have always been negative. The patient's fasting blood-sugar has never been above 0.12 per cent. and on most occasions has been below 0.10 per cent.

The record of this patient's glucose tolerance tests is as follows:

	May, 1920. Per cent.	March, 1921. Per cent.	February, 1922. Per cent.
Fasting blood-sugar	0.09	0.12	0.09
Blood-sugar one hour after glucose	0.21	0.23	0.22
Blood-sugar two hours after glucose	0.15	0.17	0.18
Urine two hours after glucose	0.5	1.5	0.7
Weight	163 pounds	174 pounds	180 pounds

Comment: In May, 1920 this patient was told that he was a case of mild diabetes, and that it was important for him to restrict the sugar content in his diet and to be careful about his weight. He has, however, persistently refused to adopt any restrictions of the diet and, furthermore, during this period of observation there has been a marked gain in weight. Despite the fact that he has been on an unrestricted diet and has gained in weight, his tolerance for sugar shows no very marked change. But it can be said that whatever change has taken place has been in the direction of a lowered tolerance. In this case it is probably fair to infer that there will be continued lowering of the tolerance for sugar unless the patient adopts measures to restrict his diet and to control his weight.

Case IV.—M. C., age fifty. Patient was admitted to the hospital in December, 1919, with a diagnosis of diabetes. At the time of entrance the fasting blood-sugar was 0.25 per cent. Patient became sugar free four days after entrance without the necessity of any starvation period. After a stay in the hospital

of two weeks the patient was discharged on a diet containing approximately 110 grams of carbohydrate, 80 grams of protein, and fat up to the caloric requirement. Her fasting blood-sugar at this time was 0.15 per cent. Between January, 1919 and March, 1920 the patient was seen repeatedly in the Out-patient Department, and at no time was sugar found in the urine and, in addition, her fasting blood-sugar returned to normal. As time went on it became impossible to keep her on a definite diet, so that in March, 1920, at the time of the first glucose tolerance test, she was eating practically as she desired.

The record for her glucose tolerance tests is as follows:

	March, 1920. Per cent.	April, 1921. Per cent.	February, 1922. Per cent.
Fasting blood-sugar	0.09	0.08	0.14
Blood-sugar one hour after glucose	0.097	0.25	0.32
Blood-sugar two hours after glucose	0.11	0.175	0.196
Urine before glucose meal	....	....	0
Urine one hour after glucose	....	....	0.5
Urine two hours after glucose	Trace	0.5	0.8
Weight	144 pounds	162 pounds	170 pounds

Comment: In March, 1920 the glucose tolerance test gave results all of which are within normal limits, but the curve shows a slight but gradual rise at the end of the first and the second hours and there is also a trace of sugar in the urine. The full significance of this result was not appreciated at the time, and because of this the patient was allowed to do about as she pleased in regard to diet until at the time of the second test in April, 1921. In this test it will be noted that there is a distinct lowering of the sugar tolerance, coincident with a gain in weight. At this time the patient was instructed as to the necessity of restricting her diet and adopting measures to control weight. Despite this, the patient has continued to eat as she desires, with the result that in February, 1922 a third tolerance test shows a still further lowering of the ability of the body to handle sugar. Note that in the first two tests the fasting blood-sugar is normal, but that in the third test the fasting blood-sugar has become abnormal. The first glucose test indicated a recovery of tolerance, and, accordingly, the patient's demand for food was

granted. Such a course was theoretically risky because of the initial blood-sugar of 0.25 per cent., and, in fact, was imprudent as evidenced by the subsequent tolerance tests. I feel that this is a very important case because it shows what harm can be done by being too easy with such a patient.

Summary of Group II.—The 4 cases above mentioned are fairly typical examples of mild diabetes in which proper diagnosis might very well present some difficulties. The importance of the proper management of this type of case can hardly be overestimated. As a matter of fact, it is probably not too much to say that such cases are even more prone to get into trouble than the case of definite diabetes. In the proper diagnosis and management of such a case the physician has a real responsibility and also a definite opportunity to practice preventive medicine. Two examples will serve to illustrate this point.

(1) Recently a patient was admitted to the hospital in diabetic coma as a result of a large carbuncle on the back of the neck. He died within a few hours after admission. His relatives tell the following story concerning his diabetes:

A few years ago he went to a physician and was told that he had a small amount of sugar in the urine, that he was a diabetic, and that he must adopt certain dietary restrictions. The patient was not content with the physician's diagnosis, so went to another physician, who told him that the urine contained no sugar and that he probably was not a diabetic. In order to be absolutely certain, he went to a third physician, who told him that he had a very small amount of sugar in the urine, but that this was a matter of no concern, inasmuch as almost everybody shows a little sugar in the urine occasionally. The net result was that the patient took no dietary precautions, gained steadily in weight, developed a carbuncle, and died in diabetic coma.

(2) A woman aged forty-seven was told seven years ago that she had mild diabetes and was advised to adopt certain slight dietary restrictions. For two or three years she adhered to directions, despite the fact that at no time during this three-year period was sugar found in the urine. Afterward she decided that the diabetes had disappeared and began to eat about as she

desired, with a resulting increase in weight. A few days before admission to the hospital she developed a small furuncle on her back, and this rapidly progressed, until at the time of admission she had a large carbuncle. At the time of admission she was in a precomatose state and both sugar and diacetic acid were present in the urine. She eventually made a good recovery.

In both the above cases the physician as well as the patient were probably at fault. (No physician has a right to make light of the presence of a glycosuria, no matter how slight or how infrequent.) Mild diabetics are important cases and require just as careful if not even more careful treatment than the severe cases.

In the group of 4 cases presented with records of tolerance tests improvement in the ability to handle sugar has been noted in 1 case, and in 2 cases there has been demonstrated lowering of the ability to handle sugar. Concerning Case I nothing definite can be said because we have only the one observation. It is my feeling that one glucose tolerance test is often of very little value. The remaining 3 cases, however, are of considerable interest because it has been possible to follow them over a period of years.

Whether or not a glucose tolerance test is the best way to study such cases is a question. In my opinion it might be better to adopt a glucose meal which would throw a smaller load on the organism, as, for example, 40 to 60 grams of glucose according to body weight. Or, if this is not possible, then less dependence should be placed upon the fasting blood-sugar and more upon a test made at a definite interval following a known meal. A prescribed meal of cereal, milk, and fruit would probably answer the purpose. Certainly the above tests show that the information furnished by a single fasting blood-sugar is of very little value.

Conclusions.—(1) Glucose tolerance studies have been presented in a few cases, illustrative of two general groups of conditions, in which the diagnosis of diabetes is not always clear.

(2) There is a condition which for lack of a better term can be called renal glycosuria and in which the presence of glycosuria is probably not of serious import. The condition is characterized

by glycosuria without hyperglycemia. Such cases must be kept under careful and constant supervision. Whether or not this condition is a clinical entity time alone will tell.

(3) Cases which show sugar in the urine only occasionally, but which show distinctly abnormal reactions following a glucose meal, are, in the absence of pathologic conditions which in themselves may give rise to glycosuria, cases of mild diabetes and should be treated as such.

(4) Cases of mild diabetes constitute a very important clinical group. Their ability to handle sugar may be definitely increased or decreased, depending upon the kind of supervision. They are always just as likely to get into serious "diabetic trouble" as the more severe type of case. Their proper management offers to the physician a real opportunity to practice preventive medicine.

(5) The relation between gain in weight and lowering of sugar tolerance is definitely shown.

(6) Glucose tolerance tests are not as valuable as claimed by some, because: (*a*) There is often considerable doubt as to whether or not a given reaction is normal; (*b*) a meal heavy in glucose may cause permanent harm; (*c*) no standard test-meal has been generally accepted.

(7) In the diagnosis and management of mild diabetes it is probable that information just as accurate can be obtained by making blood tests at given periods following an ordinary known meal or following a smaller glucose meal than the one used above.

(8) The fasting blood-sugar by itself gives only partial and often misleading information.

(9) The cases here presented are instructive because most of them have been studied over a longer period than the cases usually reported in the literature, thus making it possible to show in the blood-sugar curves, as others have shown by urinalysis and by single blood-sugar determinations, that tolerance for sugar improves with dietary obedience and falls with neglect.

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OBSERVATIONS ON IMPORTANT DISORDERS OF THE HEART BEAT[1]

IN the course of years of observation of patients in a large clinic occasional instances come to one's attention that teach more about the natural history of disease than many routine observations. Now and then there appears a patient who yields a story, or physical examination, or instrumental findings of much practical importance or of very particular interest. More and more there is being realized the value of "chronic" clinical research, that is, the chronic study of chronic disease, or of conditions of long standing. Bound up in this chronic study there lies hidden greater accuracy in forecasting a patient's future.

In recent months in the Cardiac Clinic at the Massachusetts General Hospital we have seen 8 patients who have proved particularly worthy of study and report. Three of them have illustrated points of interest in paroxysmal tachycardia—its relative unimportance in prognosis of life and activity, its relationship to auricular flutter, and the futility of administering digitalis in its treatment. Next, there are 2 patients with auricular fibrillation, one treated by quinidin, the fibrillation being abolished by this drug while ectopic beats also present persisted, and the other showing a regular ventricular action, probably a digitalis effect. A sixth case illustrates the serious prognosis so often to be associated with high-grade intraventricular block, here complicated by auriculoventricular block and ventricular escape. A seventh case is an example of the very rare condition of auricular standstill probably the result

[1] From the Cardiac Clinic of the Massachusetts General Hospital.

of digitalization. Also this patient illustrates the occurrence of varying aberration in the spread of the excitatory process in the ventricles with the T wave in Lead II of the electrocardiogram of extraordinary appearance arising high from the Q-R-S complex, quite likely a toxic effect, perhaps a uremic manifestation. There is, finally, a patient with auricular flutter who showed at first an unique bigeminal pulse, later reverting to the usual regular 2 to 1 heart-block, changed by digitalization to higher grades of block and to auricular fibrillation.

Case I. S. K. A Case of Paroxysmal Tachycardia Needlessly Given Digitalis, with the Production of Sino-auricular Heart-block.—The patient is a Russian Jewish housewife of twenty-nine, referred to the Cardiac Out-patient Department complaining of attacks of palpitation and "skipping of beats."

Present Illness.—For the last two to three months she has had frequent attacks of palpitation lasting from five to ten minutes. These attacks come on and pass off very quickly, the heart rate changing from a slow to rapid, or rapid to slow rhythm within a few seconds. During the last few months she has been working hard and has been more nervous than usual. She has noticed that the attacks are apt to come on when she is nervous or when she "thinks about her heart." Otherwise they may come on at any time of the day without particular relation to meals or exertion. During the attack the heart is regular; she may be short of breath or note no discomfort except worry about the condition. Between attacks there are no cardiac symptoms.

In addition, during the last few days she has noted that her heart frequently "skips beats"; this worries her even more than the attacks of palpitation. Her physician has been giving her two tablets of digitalis daily (probably digifolin or digitan) for the last two months, and sends her to the hospital for "an obscure, apparently nervous heart action."

Past History.—Diphtheria in childhood; no tonsillitis, chorea, scarlet fever, or rheumatism. She has always been healthy. Her appetite has been poor for the last two to three months. Otherwise the past history is entirely negative.

Marital history, family history, social history, and occupational history contain no significant facts.

Physical Examination.—"The patient is a well-developed and nourished, healthy looking woman of twenty-nine. The physical examination is completely negative except as noted below. There is no evidence of thyroid disease or syphilis."

"Heart: The apex impulse is seen and felt in the fifth space, 8 cm. to the left of the midsternal line and slightly inside the midclavicular line. Percussion shows no enlargement to left, to right, or in the region of the great vessels. A short, soft systolic murmur, not obscuring the first sound, is heard at the

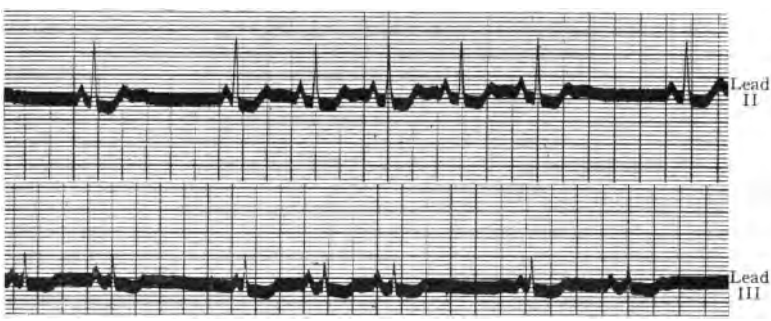


Fig. 278.—Electrocardiogram (Leads II and III) of S. K. "Sino-auricular block" and inverted T. A digitalis effect. (In this and following figures abscissa = 0.2 second, ordinate = volt 10^{-4}.)

base. There are no other murmurs; the quality of the sounds is not abnormal. There is moderate respiratory arhythmia, and, in addition, an occasional pause not quite equal to two normal intersystolic intervals. During this pause no premature beat occurs. This arhythmia is distinct from the respiratory arhythmia. Pulse 60 to 70. Blood-pressure: systolic 132, diastolic 92. Urine negative. Hemoglobin 80 per cent."

The electrocardiogram (Fig. 278) shows a marked sinus arhythmia, with occasional "sino-auricular block" and ventricular escape. The T wave is diphasic. There is no auriculo-ventricular block nor any premature beats.

Discussion.—Here we have a nervous, but otherwise healthy

young woman, who comes to us worried about "heart trouble." Her attacks of palpitation during the last three months are undoubtedly those of paroxysmal tachycardia. The digitalis she has received, evidenced in the electrocardiogram by the diphasic T wave, has accentuated her previously existing sinus arhythmia to a "sino-auricular block," a rather uncommon effect, but one that is important only as an indication for the cessation of digitalis. There is no evidence of any endocardial or myocardial disease; there is here no indication for digitalis; it may even increase the frequency of the paroxysms of tachycardia. The etiology of these attacks is essentially extracardiac, acting through the nervous control of the heart. The principal therapy in this case is reassurance; she must be convinced that there is nothing of consequence wrong with her heart. Her régime of living must be so adjusted that her nervous tension is reduced to a minimum. Provoking factors for the attacks must be sought and eliminated. Drugs are to be avoided, though bromids may be of temporary use. The value of quinidin sulphate in paroxysmal tachycardia is as yet unproved, and will be referred to in a succeeding case.

All drugs were omitted and the situation carefully discussed with the patient. Three weeks later she reported feeling very much improved. She had had no attacks of tachycardia and after a few days had noted no "skipped beats." Examination showed a normal cardiac mechanism.

Case II. G. T. Paroxysmal Tachycardia Occurring at Frequent Intervals for Twenty-five Years in a Man Constantly at Hard Physical Labor.—The patient is a single white man of sixty-one, referred to the Cardiac Clinic of the Out-patient Department for the relief of attacks of palpitation. By occupation he was formerly a coal teamster and is now an ice teamster.

Present Illness.—For twenty-five years he has had periodic attacks of palpitation, usually at intervals of a week. He states that each attack comes on very suddenly, so that within a few seconds the heart is beating at a very rapid rate. The rapid onset may "knock him down" if he is not holding on to something; at other times he hardly notices it. Originally the attacks

were very brief, for he could stop them by holding his breath after full inspiration. They now last from a few minutes to fifteen hours, but average about ten hours. Commonly they appear at night, waking him up from sleep, and rarely come during the day. There may be no discomfort throughout the attack; occasionally, however, there is a sense of constriction in the throat, slight dyspnea, flushing of the face, and an aching in the right shoulder. The heart has at all times been regular. He has never had any cough, edema, or cyanosis. The next day he is tired from lack of sleep, as the palpitation usually keeps him awake. But he thinks that if it were not for the lack of sleep he would be unaffected by the attacks.

Between attacks there are no cardiac symptoms. He has always been able to do the work of two men, and though his present job involves heavier work than his previous one, he has no difficulty in carrying on the hard exertion required so long as he gets enough sleep. Recently the attacks have been somewhat more frequent and occasionally appear during the day. Still he is not at all disturbed over his condition.

For the last twelve years he has been an occasional attendant at the general out-patient clinics for minor injuries or illnesses. During this period the attacks of palpitation were noted, but did not appear of sufficient importance to the patient or examiners to demand attention. During this whole period the cardiovascular system was negative to physical examination.

Past History.—Patient states he has always been strong and healthy. He has never had any rheumatic infections and denies venereal disease by name and symptoms. Aside from a fractured patella in 1911, flat-foot, and varicose veins with ulceration in the same year, the past history is essentially negative.

Occupational History.—He has been engaged in heavy physical labor all his life, with lifting and carrying considerable weights.

Habits.—The patient states that he has been a heavy smoker all his life. Tea, coffee, and alcohol negligible.

Physical Examination.—"The patient is a powerfully devel-

oped and well-nourished, healthy looking man of sixty-one. There is moderate arcus senilis and the pupils are slightly irregular, though they react well to light and distance.

"The chest is thick and round. The lungs are emphysematous.

"Heart: The apex impulse is seen and felt in the fifth space 10.5 cm. to the left of the midsternal line. By percussion the apex is 11 cm. to the left in the fifth space. There is no apparent enlargement to the right or any apparent increase of the supracardiac dulness. The sounds are of good quality and regular except for an occasional premature beat with compensatory pause. There are no murmurs. The pulses are equal, with good tension and volume. The radials and brachials show slight hardening, but no tortuosity. Pulse 70. Blood-pressure: systolic 150, diastolic 90.

"There are varicose veins in both legs and a few scars of healed varicose ulcers."

Otherwise the physical examination was completely negative.

The urine and blood Wassermann were negative.

The electrocardiogram showed normal rhythm except for a few ventricular premature beats. There was marked left ventricular preponderance. Rate 63.

Discussion.—For twenty-five years this man has had frequent attacks of what is undoubtedly paroxysmal tachycardia. In contrast to the apprehensiveness of the woman in the preceding case, these attacks have not worried him in the least. He has continued steadily at hard lobar and comes to us now only because their increasing frequency disturbs his sleep. Suppose that twenty-five years ago, when his first attack occurred, he had been told that he had "a bad heart" and that he must quit work—what an economic loss to the community it would have been! But now that he is sixty-one years old, we must be a little more careful in prognosis than we would have been in his case twenty-five years ago, or than we were in the preceding case discussed. Probably he will live a number of years yet at hard work despite the attacks; still he has evidence in the arcus senilis and peripheral arteries of general

arteriosclerosis. His heart is somewhat enlarged; the electrocardiogram shows marked left ventricular preponderance. Most probably he now has some degree of cardiosclerosis—possibly not more than the average male of his age. There is a possibility that auricular fibrillation or auricular flutter may appear following or independent of an attack of paroxysmal tachycardia. The relationship between paroxysmal tachycardia and the circus movement of fibrillation and flutter has not yet been established, but occasionally flutter follows paroxysmal tachycardia, as will be shown in the next case. For the present it is considered advisable for him to continue his work and tobacco; he is ordered to take 0.2 gram of quinidin sulphate twice daily. This is purely experimental therapy, this case being one of a series in which the effect of the drug is being tried. The patient will be followed rather closely and the therapy will be varied as indicated. Bromids, hypnotics at bedtime, limitation of activity, and so on, may later be valuable procedures. Digitalis is not indicated. At his age tobacco restriction hardly seems to offer anything.

Five weeks later the patient returned, stating that the attacks had been shorter and less frequent—that he felt that the quinidin was helping him. Of course, no conclusions as to the efficacy of quinidin in this case can be drawn from so short a period of observation.

Case III. F. B. P. A Case of Paroxysmal Auricular Flutter of Eight Years' Duration, Recently Showing Alternate Flutter and Auricular Paroxysmal Tachycardia.—A single, white female of forty-six entered the hospital March 11, 1922 for relief of an attack of tachycardia. Occupation, nurse.

Present Illness.—For the first time, in the fall of 1913, the patient had an attack of heart trouble diagnosed by her doctor as "tachycardia." This first one was of short duration, but during the following couple of months she had frequent attacks, which resulted in such weakness that she was in bed for seven months.

In December, 1914 she reported for the first time to the Out-patient Department, and since that time has been followed

constantly in the Out-patient Clinic and during several admissions to the wards. The description of the attack has been generally quite similar from that time to the present. Usually the heart suddenly begins to beat rapidly. The rhythm has always been regular except once, when an absolute arhythmia proved to be auricular fibrillation by electrocardiogram. There is increasing weakness and some dyspnea. In the first attacks she felt that she "was going to die." Finally, the attack passes off rather slowly. Often the pulse remains as high as 120 for several hours after an attack. She is left weak, worn out, and sore over the precordium. The attacks last from a few minutes to several days and occur at intervals varying from hours to months. Electrocardiograms have been taken during a large number of these attacks. During the whole period, up to the time of the present admission, they have showed auricular flutter (except for the one attack of fibrillation referred to previously). The auricular rate usually ranges from 220 to 280 per minute and the ventricular rate from 120 to 240, the higher ventricular rates representing the periods when there is no auriculoventricular block. Once a ventricular rate of 273 was recorded, a print of which has been published.[1]

During the first year or two the patient was urged markedly to limit her activity. During the latter years, however, she has worked fairly steadily at nursing, and undoubtedly has been better with such activity than without it. Occasionally after a period of prolonged attacks she has been forced to give up work for a week or two, but rarely for a longer period.

At intervals since 1914 complete careful physical examinations, with *x*-ray and other laboratory studies, have failed to reveal any pathology except as noted below. Neurologic examination by the nerve department has been constantly negative except for indefinite findings suggestive of "involvement of the sympathetic nervous system." Except for the tachycardia during an attack the cardiovascular system has been consistently negative to physical examination. It was not until 1919 that the *x*-ray showed slight transverse enlargement. A careful search has been made for extracardiac irritation,

focal infection, and so on. In December, 1915 a right cervical rib was removed as a possible irritant, clearing up a condition of the right hand closely resembling Raynaud's disease. For a few months after this the tachycardia was less frequent, but later returned to its average frequency.

At the present time she entered the hospital for the relief of an attack of tachycardia that began five days previously. As advised, she had taken at the onset 2 grams of quinidin sulphate in divided doses without apparent effect.

Fig. 279.—Electrocardiogram of F. B. P.: A, Auricular paroxysmal tachycardia, rate 173 (Lead II). B, Auricular flutter. Auricular rate = 210, ventricular = 105. C, Normal rhythm (Lead II).

Physical Examination.—"The patient shows no obvious discomfort, orthopnea, or cyanosis on admission. The physical examination is completely negative except for the heart, which is rapid and regular at 180 per minute. The sounds are of good quality; there are no murmurs. No enlargement can be made out by percussion. There is no peripheral arteriosclerosis and no evidence of congestive failure." Pulse 180. Blood-pressure: systolic 120, diastolic 70. Urine and blood negative.

The electrocardiogram (Fig. 279, A) at 4.30 P. M. on the afternoon of admission showed auricular paroxysmal tachycardia with a rate of 173. At 9.30 the same evening the apex rate had dropped to 120 per minute, still remaining regular. An electrocardiogram (Fig. 279, B) shortly after showed auricular flutter with a ventricular rate of 105 and an auricular rate of 210.

The patient was given complete rest in bed and digitalis folia, 0.2 gram three times daily, were ordered. The next morning the apex rate was again high, at 190, probably due as before to paroxysmal tachycardia. The evening of this day the rate dropped to 120, flutter again being present. The following day paroxysmal tachycardia with a rate of 190 was present in the morning, and in the afternoon a flutter with ventricular rate of 120. Finally, some time during the night, the apex rate dropped to 90 and an electrocardiogram (Fig. 279, C) in the morning showed normal sinus rhythm. The patient was then discharged relieved.

Discussion.—This case is interesting from several points of view. A young woman without etiology for heart disease (except possibly tonsillitis) and without any objective evidence of cardiac disease except the slight enlargement made out only by *x*-ray, began having attacks of paroxysmal auricular flutter at the age of thirty-seven. Except for the short period of freedom following the excision of the cervical rib in 1915 they have continued to the present time without becoming permanent, and without producing any marked limitation in her activity. Careful study of the general physical condition reveals no significant facts. She is decidedly better at work than when prevented from working. Finally, in this last attack we have the interesting transitions from auricular paroxysmal tachycardia to flutter. It is quite likely that the focus in the auricle responsible for the generation of ectopic rhythmic impulses at 170 to 180 per minute producing the paroxysmal tachycardia increases its rate until, when it reaches about 200, it acts similarly to Lewis' artificial stimulation in dogs' hearts[2] and sets in action the circus movement that is responsible for flutter.

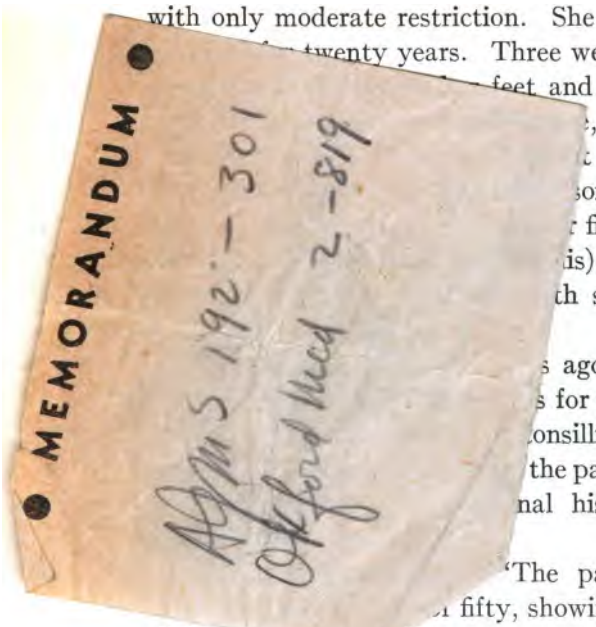
Therapy in this case has been discouraging. Limitation of

activity, bromids, change of environment, and so forth, have all proved ineffective. Quinidin, so far as it has been tried, has proved of no value. It would seem that we can do little further for this patient, at least for the present.

The remaining 5 cases present definite "organic" heart disease with points of interest worth discussion.

Case IV. L. M. H. Rheumatic Heart Disease with Mitral Stenosis, Auricular Fibrillation and Ectopic Beats; Persistence of the Ectopic Beats After Restoration of Sinus Rhythm by Quinidin.—The patient, a single white woman of fifty, enters the hospital January 24, 1922 for the relief of dyspnea and edema. Occupation, housework.

Present Illness.—Since an attack of rheumatic fever twenty years ago she has complained of moderate dyspnea and palpitation on exertion. There has been no hemoptysis or precordial pain, and until recently she has been able to carry on her work with only moderate restriction. She thinks her heart has been twenty years. Three weeks ago, for the first time, feet and legs and began to cough; , but for the last few days of frothy mucus sputum, ome nocturia and increased first gave her a liquid medi- is), and later some capsules th some relief, but despite it



s ago she had rheumatic fever s for the greater part of a year. onsillitis, but no chorea, scarlet the past history is not important. nal history, social history, and

'The patient is a rather obese, fifty, showing obvious dyspnea on the slightest exer... The tonsils are large and ragged, but show no redness or exudate. The thyroid is not enlarged.

"Heart: The apex impulse is seen and felt in the fifth

space 9½ cm. to the left of the midsternal line, without thrill. Percussion measurements show the apex in the fifth space 10 cm. to the left of the midsternal line, the right border in the fourth space 4 cm. to the right of the midsternal line and no evidence of increased supracardiac dulness. The sounds are of fair quality. There is an arhythmia consisting of bigeminy, the pairs of beats separated by varying intervals. There is a loud systolic murmur heard over the whole precordium, maximal at the apex, and there obscuring the first sound. In the longer pauses there is a distinct middiastolic murmur at the apex.

"The pulses are equal, but irregular, with variation in force from beat to beat. At times the alternate beat of the pair fails to reach the radial artery. The arteries are palpable, but not tortuous.

"The liver dulness extends from the fourth rib to 4 cm. below the costal margin. There is moderate edema of both legs. Otherwise the physical examination is negative."

Urine negative. Renal function 40 per cent. Wassermann negative. White blood count 9600 cells per cubic millimeter.

x-Ray showed a heart considerably enlarged both to right and left. The supracardiac dulness is not abnormal. The transverse diameter of the heart is 16.8 cm., as compared with an internal chest diameter of 28.6 cm.

An electrocardiogram (Fig. 280, A) showed auricular fibrillation, ventricular rate 100; periods of bigeminy due to ectopic beats; T wave flat; rather small complexes in all leads.

Diagnosis.—The diagnosis in this case was obviously rheumatic heart disease with mitral stenosis and regurgitation, auricular fibrillation, ectopic ventricular beats, and failure of the congestive type. It is felt that every cardiac diagnosis should be expressed in a form similar to this, in order that the diagnosis shall show the etiologic, functional, and structural type of case in hand. The old method of putting down simply "mitral stenosis," "auricular fibrillation," or "decompensated heart" is inadequate and should not be continued,[3] as it lends to careless diagnosis and incomplete understanding of the pathology.

Treatment.—The bigeminy in this case is of interest, as it

led more than one person to fail to recognize the fibrillation. In view of the bigeminy, the low T wave in the electrocardiogram, and the relatively slow rate, it was considered that the patient was probably sufficiently digitalized at entrance and might possibly be getting some toxic effects of the drug, even in the absence of nausea and vomiting. Hence no drugs were administered during the first six days after entrance. Under rest and hypnotics as needed the dyspnea decreased and the edema cleared up quite rapidly, though the begeminy persisted with little change. On the seventh day after admission she

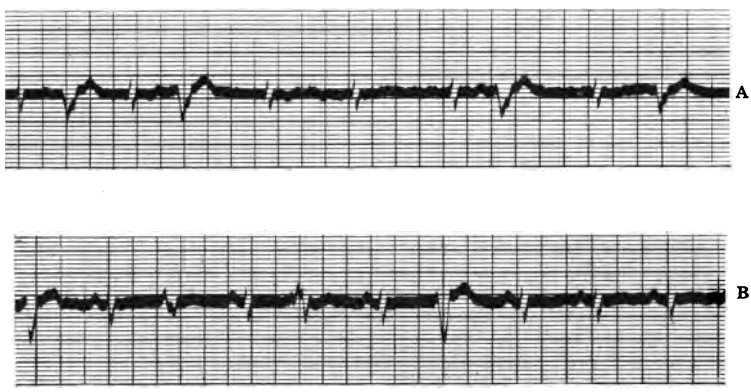


Fig. 280.—Electrocardiogram of L. M. H. (Lead II): A, Auricular fibrillation, periods of bigeminy due to ectopic beats, flat T wave. B, Normal rhythm, premature beats.

was given two doses of 0.2 gram each of quinidin sulphate at 2 and 4 in the afternoon, as test doses for hypersensitivity to the drug. For the following two days she was given five doses daily of 0.4 gram of quinidin at two-hour intervals. On the morning of the fourth day of quinidin, after 4.4 grams in two and one-half days, the electrocardiogram (Fig. 280, B) showed normal sinus rhythm interrupted by periods of bigeminy due to premature beats. Without the electrocardiogram it was difficult to be sure that there had been any change in the rhythm. The morning of the day following the restoration of normal rhythm fibrillation recurred. The twenty-four hours or less of

sinus rhythm induced by quinidin neither improved nor harmed the patient. She was then given moderate dosage of digitalis, and left the hospital much improved on February 17th.

Discussion.—It is impossible here to enter into an extended discussion of the value or danger of quinidin therapy. This case is one of a series of over 60 cases of auricular fibrillation to which the drug has been given at the Massachusetts General Hospital—a series that is to be reported in detail at a later date. This case represents a fairly large group in which quinidin restores normal rhythm for only a few hours and without benefit, though without harm, to the patient. Quinidin therapy should be considered as still in the experimental stage. If used in unselected cases serious damage and even death may, though rarely, result from embolism or fixed flutter, as balanced against benefit in the form of clinical improvement to other cases. Though a number of cases are definitely helped, whether or not this benefit justifies the risk will depend largely upon our gaining a knowledge of the type of case favorable for restoration and our ability to avoid the case in which embolism is likely to occur. So far as we can judge from present experience, it should be given only to cases without recent failure, without infection, and with fibrillation of recent onset.

In this case the persistence of ectopic beats after the abolition of the circus movement of auricular fibrillation (absolute arhythmia) is of interest, particularly as quinidin has been claimed to be of clinical value in causing the disappearance of ectopic beats.[4]

Case V. C. M. Rheumatic Heart Disease with Auricular Fibrillation and a Regular Ventricular Rhythm Due to Digitalis.—The patient is a white man of forty-nine, admitted to the hospital February 20, 1922, complaining of dyspnea and ascites. Occupation, freight handler.

Present Illness.—The patient states that he was entirely well until eight years ago, when he gradually became short of breath on exertion. This increased until he became cyanotic as well on any usual activity. Nevertheless, he was able to continue work until three years later, when he became decidedly

worse, with dyspnea, palpitation, and edema of the feet. At this time he entered a hospital, where, after treatment for one month, he improved enough to return to work. Similar "breaks in compensation" occurred at intervals of about six months during the following four years, with periods between these during which he was able to work.

Five months before entrance he again became increasingly dyspneic, with swelling of feet, abdomen and scrotum, palpitation, and precordial pain. During this period he has been taking "all kinds of strong medicines" without any relief.

Past History.—Patient states that he had excellent health up to the onset of the present illness. Typhoid fever thirty years ago. No rheumatic infections. Past history otherwise not significant.

Marital history, family history, social history, and occupational history not important.

Habits.—He has used either a pipe or cigars "all the time" and commonly takes 3 or 4 glasses of whisky daily.

Physical Examination.—"He is a well-developed and nourished man sitting propped up in bed, evidencing dyspnea on slight exertion, with mitral facies and cyanosis of the lips.

"The physical examination is negative except as noted below.

"The tonsils are clean, small, and not reddened. The thyroid is not abnormal. There are medium and fine moist râles at both bases. There is marked ascites and edema of the legs, scrotum, and back.

"Heart: The apex impulse is seen and felt in the fifth space 13 cm. to the left of the midsternal line without thrill. The heart is absolutely irregular and slow at 70 per minute. The sounds are of good quality. At the apex there is a long, blowing systolic murmur, obscuring the first sound, and a short mid-diastolic murmur. Both murmurs are maximal at the apex; the systolic is transmitted to the axilla and left back. The second sound at the apex is not abnormal. The pulmonary second sound is greater than the aortic second and is accentuated. There is no Broadbent's sign; the heart shifts with change in

position. To percussion the heart is enlarged to the left and slightly to the right, but no evidence of increased supracardiac dulness is made out.

"The pulses are equal, irregular, of low tension and volume. The arteries are not palpable. Pulse, 70. Blood-pressure: first systolic sound 146; last diastolic 118."

Urine, renal function, blood nitrogen, blood Wassermann, white count, stools, and blood-picture were not abnormal. *x*-Ray of the heart showed marked enlargement in all diameters, with marked prominence in the region of the left auricle.

The diagnosis was made of rheumatic heart disease with mitral stenosis and regurgitation, auricular fibrillation, and marked failure of the congestive type.

On the day of admission 8000 c.c. of fluid were withdrawn from the abdomen. Morphin, limitation of fluids, and digitalis were ordered. Next morning, after having received 0.3 gram of digitalis in the hospital, the heart was regular at 60 per minute. Electrocardiogram (Fig. 281, A), however, showed auricular fibrillation—rate 63, complete A-V dissociation, intraventricular heart-block, and diphasic T wave.

Discussion.—Here is presented the apparent anomaly of a heart whose auricles are fibrillating, yet whose ventricles are quite regular and slow. This is undoubtedly a digitalis effect. Without question he had been receiving considerable quantities of digitalis previous to his entrance to the hospital, enough, certainly, to slow the heart to 60. The additional 0.3 gram of a potent preparation given in the hospital probably not only increased the auriculoventricular block, but produced an irritability of the A-V node, so that the ventricles no longer responded to impulses coming from the auricles, but assumed their own independent "idioventricular" rhythm, presumably in response to impulses arising in the A-V node. The diphasic T wave is additional evidence of digitalization.

It was assumed that the patient had, for the time being, received all the possible benefit from digitalization and might be getting toxic effects from overdosage. Hence the digitalis was stopped. In the next few days he steadily improved and

the edema began to disappear. How much of this improvement was due to the administration or to the cessation of digitalis can only be conjectured. By February 24th there was definite ventricular arhythmia, and the electrocardiogram (Fig. 281, B) showed auricular fibrillation without A-V dissociation.

To determine the effect of digitalis the drug was resumed, and after 0.4 gram idioventricular rhythm again appeared. On omitting digitalis again ventricular arhythmia reappeared. The patient steadily improved and was discharged relieved.

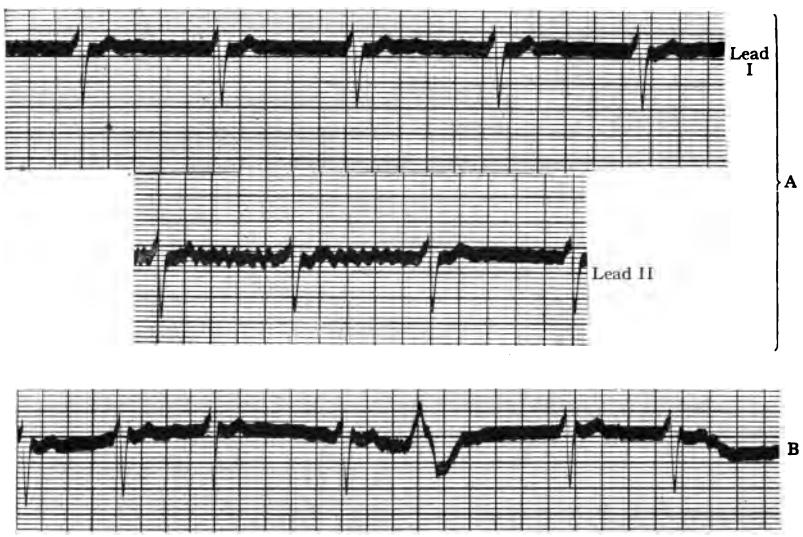


Fig. 281.—Electrocardiogram of C. M.: A, Auricular fibrillation, complete A-V dissociation, aberration, diphasic T wave (Leads I and II). B, Auricular fibrillation without A-V dissociation (Lead II).

The establishment of idioventricular rhythm under digitalis in cases of auricular fibrillation has been reported occasionally, notably by Thomas Lewis,[5] who was one of the first to observe it. Probably the careful following of cases by electrocardiograms would prove it to be more common than is at present suspected. Possibly some of the cases in which digitalis is said to have restored normal rhythm from auricular fibrillation have really been cases in which A-V dissociation resulted in a regular

ventricular rhythm without any change in the fibrillation of the auricles.

Case VI. C. H. H. Rheumatic Heart Disease with Mitral and Aortic Involvement, Premature Beats, Auriculoventricular Block, Bundle Branch Block, and Ventricular Escape.—This patient was a white American male of fifty-two, entering the hospital January 10, 1922, complaining of dyspnea and weakness. Occupation, contractor.

Present Illness.—Twenty years ago following a long swim the patient coughed up small quantities of frothy, blood-tinged sputum for several days. Since then this has occurred twice, each time after hard work. For the last twenty years he has had a peculiar sharp pain just below the thyroid cartilage whenever he climbed a short grade, and has noticed slight but increasing dyspnea on exertion. For the last five years he has needed two pillows at night. For six years periodic attacks of exhaustion have forced him to stay at home for a few days at a time. Nevertheless, until the last two months he has been very busy and doing hard work. Since that time he has been unable to work because of weakness, dyspnea, occasional vertigo, and attacks of nocturnal dyspnea. He has noticed an occasional "thump" of the heart. He has not been forced to remain in bed and has walked into the hospital.

Past History.—Measles and chickenpox in childhood. He was uncertain about diphtheria and scarlet fever and remembered no rheumatic infections.

Family history, social history, marital history, and occupational history unimportant.

Habits.—He had been a constant user of tobacco all his life. Coffee, tea, and alcohol negligible.

Physical Examination.—"The patient is a well-developed and nourished man of middle age, showing dyspnea on exertion, but no cyanosis. The physical examination is negative except as noted below. There are a few moist râles at both bases of the lungs, but no edema, ascites, enlarged liver, or hydrothorax.

"Heart: The apex impulse is seen and felt in the fifth space 13 cm. to the left of the midsternal line. By percussion the

left border is 14.5 cm. in the fifth space, and the right border in the fourth space 3 cm. to the right of the midsternal line. No increase in the supracardiac dulness is made out. The sounds are distant and of poor quality. There is an irregularity apparently due to extrasystoles. There is a high-pitched systolic apical murmur partly obscuring the first sound and a faint mid-diastolic murmur, also at the apex. A short, faint early diastolic murmur is made out over the fourth left interspace just to the left of the sternum. The aortic and pulmonary second sounds are not accentuated. The pulses are equal and of fair tension and volume. The arteries are not palpable. Pulse, 85. Blood-pressure: systolic 130, diastolic 90."

Urine, white count, blood Wassermann, blood-smear, and stool are not abnormal.

x-Ray showed that "the heart shadow is enlarged in all diameters, the shadow of the left ventricle predominating and showing distinct blunting of the apex. The supracardiac dulness is increased. There is definite prominence of the aortic shadow to the right. The appearance is that of multiple valve lesion with hypertrophy of the left side of the heart and dilatation of the arch." Measurements on the "seven-foot plate" confirmed these findings.

The electrocardiogram (Fig. 282) showed right bundle branch block, partial A-V block, A-V nodal premature beats (ventricular escape), ventricular premature beats, P-R interval = 0.30 to 0.35 second.

Discussion.—A diagnosis was made of rheumatic heart disease with mitral and aortic involvement, bundle branch block, partial A-V block, premature beats, and slight congestive failure. In view of the dilated aorta and his age, it was considered that there was, in addition, some degree of arteriosclerosis. The block could be accounted for rather more readily upon this basis than on the basis of a rheumatic heart in this particular case.

What is the prognosis? A man of fifty-two, who has had slightly progressive symptoms for twenty years, finally gave up work two months before entrance. Yet he was well enough

to walk into the hospital and showed no obvious congestive failure except the râles in the lungs. He has had no angina. Upon the face of it one would not be inclined to take a very serious view of his condition at entrance to the hospital. But several factors stood out as danger signals in the prognosis.

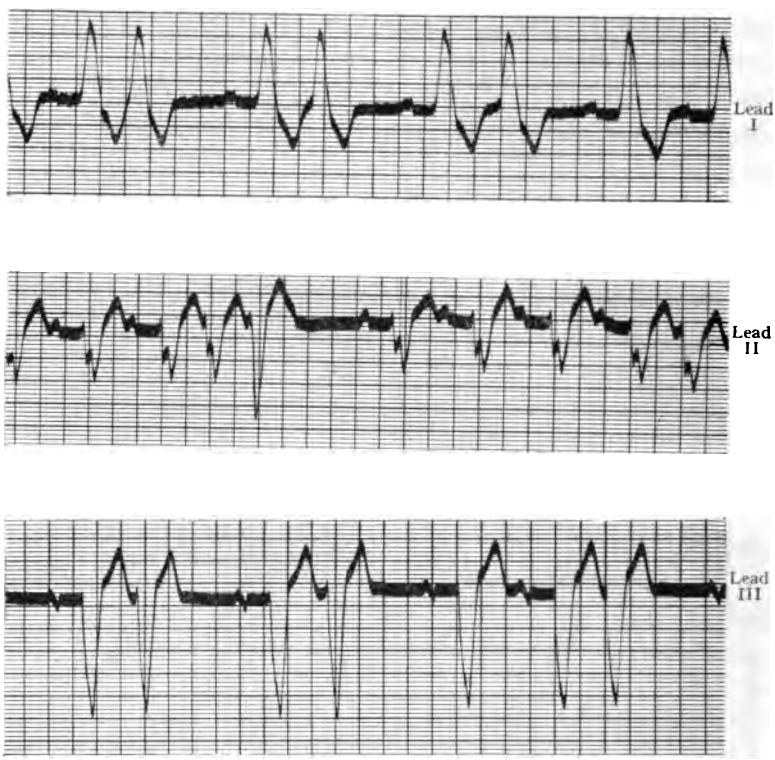


Fig. 282.—Electrocardiogram of C. H. H. Right bundle branch block, partial A-V block, A-V nodal premature beats (ventricular escape), ventricular premature beats (Leads I, II, and III).

His heart sounds were of very poor quality, especially the first sound at the apex; this we believe to be a fairly reliable sign of myocardial exhaustion. Then the electrocardiogram showed extensive blocking, together with myocardial irritability expressed in premature beats. The bundle branch block, in par-

ticular, we believe to be evidence almost invariably of widespread myocardial damage. In a series of cases of bundle branch block being followed in this clinic 22 out of the 29 upon whom data is complete have died, usually within a few weeks to a couple of years from the time the bundle branch block was first observed. Also in this patient the cardiac enlargement was extreme. Considering these findings and despite evidence of any marked congestive or anginal failure, he was given a poor prognosis.

Morphin, bromids, and hypnotics were administered as needed. Digitalis leaves, gram 0.1, were given three times daily for two days, but seemed to increase the block and symptoms and were therefore omitted. He grew steadily worse. On the morning of the ninth day after entrance he developed a fever and showed many râles at both bases. The next morning there was evidence of thrombosis (probably embolic) in the left little finger and a red spot on the conjunctiva of the right eye. The same evening he developed a right hemiplegia, and, on the following morning, consolidation at the base of the left lung. On the morning of the thirteenth day in the hospital he died of cardiac failure and multiple embolism.

The combination of extensive blocking of the conduction system of the heart with premature contractions from two foci made the case one of considerable interest from the viewpoint of cardiac mechanism. From a clinical point of view the relation of electrocardiographic findings to prognosis was of interest.

Case VII. G. S. Uremia; Hypertensive Heart Disease; Auricular Standstill, Probably Due to Digitalization, Changing to Auricular Fibrillation and Sino-auricular Tachycardia.—A single man of forty-three, by occupation a marine engineer, entered the hospital November 10, 1921, complaining of dyspnea.

Present Illness.—Eighteen months before entrance he was suddenly seized with a severe frontal headache and a little numbness in the left arm and leg; the next morning he was unable to move that arm. The left leg, though numb and weak, did not prevent him from walking. He thought his mouth

was pulled over to the left, and the vision of his right eye impaired. After being in bed for three months the paralysis gradually cleared up. Following this he had occasional frontal headaches and became gradually weaker and dyspneic on exertion. One year ago he was told by his physician that his heart and kidneys were unaffected, but that he had a very high blood-pressure. Because of his steady increase in weakness and dyspnea he came to the hospital for treatment. There had been no renal symptoms.

For ten days prior to entrance he had been taking a tablespoonful of infusion of digitalis four times daily. The day of entrance he was given in the hospital three ampules of digifolin hypodermically.

Past History.—Measles and scarlet fever at the age of five. Venereal disease denied by name and symptom. No rheumatic infections. Past history otherwise completely negative.

Occupational, social, and family history unimportant. Habits good.

Physical Examination.—"The patient is a cyanotic, somewhat stuporous man, obviously very ill. The pupils are equal and react sluggishly to light and distance. The mouth, throat, and neck are not abnormal. At the bases of both lungs are medium moist râles and impaired breath sounds.

"Heart: The heart is markedly enlarged both to right and left, but with no increase in the supracardiac dulness. The sounds are of fair quality and regular at 110 per minute. No murmurs are made out.

"The pulses are equal, regular, synchronous, and of good tension and volume. Pulse 110. Blood-pressure: systolic 200, diastolic 110. The abdomen and extremities are negative."

The fundi of both eyes showed disk outlines blurred and hazy, with a definite papillo-edema. No retinal hemorrhages were seen, but scattered patches of exudate in both eyes. In the left eye below the disk was seen a bright white streak stretching away in an undulating line, possibly a thrombosed vessel. Diagnosis of eye consultant: Albuminuric retinitis.

Urine: Specific gravity 1010 to 1012, large trace of albumin;

the sediment showed many white blood-cells and occasional casts. Non-protein nitrogen = 99.9 mgm. per 100 c.c. of blood. Renal function 0 per cent. in two hours and ten minutes. Wassermann negative. Stool negative.

The diagnosis was obviously uremia and hypertensive heart disease with congestive failure. The usual procedures for treatment were instituted.

The day after entrance the heart rate dropped to 80; no further digitalis was given. Nevertheless, the rate steadily dropped until on the afternoon of the seventh day after entrance it had reached 40. No irregularity was noted at any time dur-

Fig. 283.—Electrocardiogram of G. S. Auricular standstill, ventricular escape, and intraventricular block (Leads II and III).

ing this period. An electrocardiogram (Fig. 283) taken the following morning revealed a very interesting condition. The ventricles were beating regularly at 55, while there was no evidence whatever of any auricular activity. In addition, intraventricular block was in evidence, with marked variation in the Q. R. S. complexes and in the T wave. Polygrams showed no evidence of auricular activity. The diagnosis was, therefore, made of auricular standstill with ventricular escape and intraventricular block.

Discussion.—Auricular standstill is one of the unusual effects of digitalis upon the heart. Such a condition has been

produced experimentally in the cat by depression of the sino-auricular node and of the junction between the atrioventricular node and auricle.[6] In 1916 3 clinical cases were reported from this hospital.[7] In all of these cases digitalis had been given, and in all auricular activity reappeared when the digitalis intoxication had worn off. Lewis,[8] also, has reported a case of auricular standstill, but did not state whether or not digitalis had been given.

We expected that when the delayed cumulative action of the digitalis had disappeared, auricular activity would reappear.

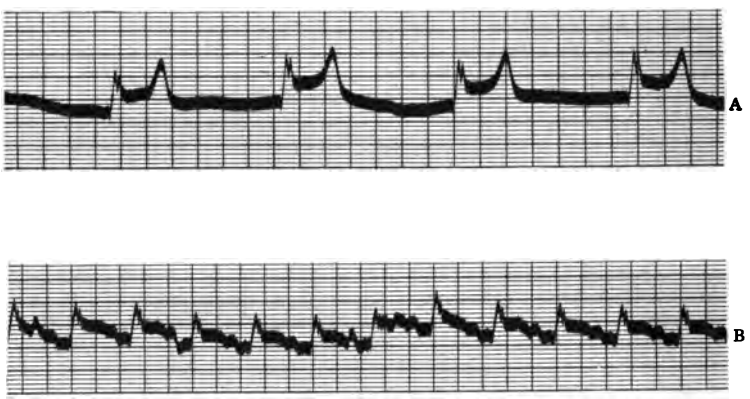


Fig. 284.—Electrocardiogram of G. S.: A, Similar to Fig. 283, the T wave arising from a point higher on the Q-R-S complex (Lead II). B, Sino-auricular tachycardia, intraventricular block (Lead II).

And such proved to be the case. After many changes in the shape of the various complexes from day to day, on November 24th, fourteen days after entrance, and six days after the auricular standstill was first noted, evidence of auricular activity was first seen in the electrocardiogram. Since ventricular arhythmia was found, auricular fibrillation was now considered to be present. The next day this was more marked.

During this period the patient had developed definite uremic coma and pericarditis with moderate effusion. On the morning of the 26th the apex rate rose to 120 and was again regular. An electrocardiogram (Fig. 284, B) showed sino-auricular tachy-

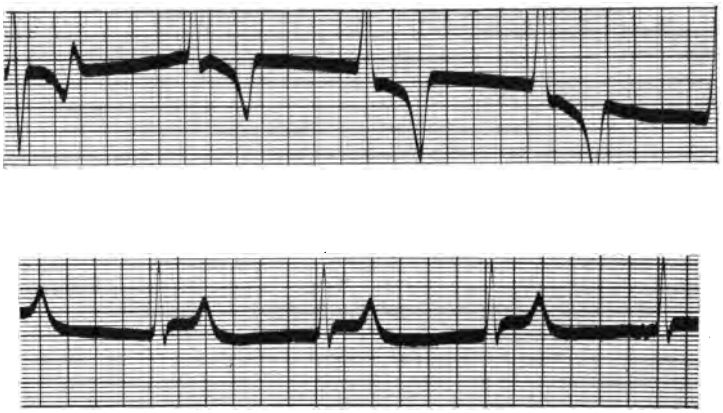


Fig. 285.—Electrocardiogram of G. S. Similar to Fig. 283 (Lead I).

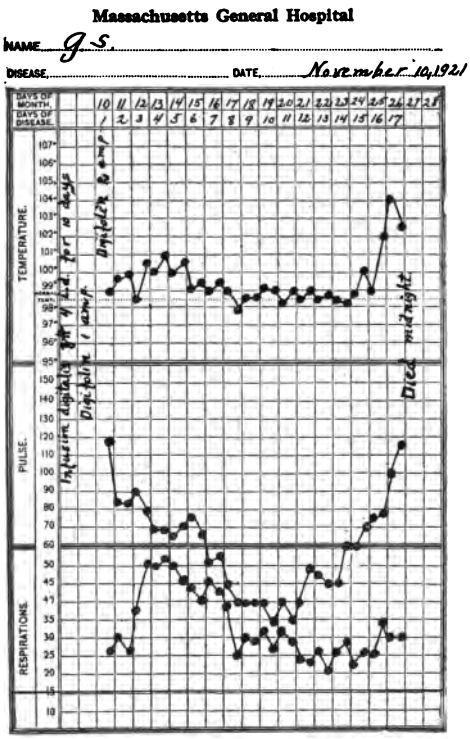


Fig. 286.—Clinical chart of G. S.

cardia. The patient was at this time moribund and died at midnight of that day.

The auricular standstill in this case should not be considered the result of uremia *per se*, as it certainly appears in the absence of uremia and is probably no more common in it than in other cases of diseased or toxic heart muscle. The standstill of the auricle should be considered as due to the effect of digitalis upon an injured myocardium.

Disturbances of mechanism are not uncommon in uremia, but digitalis nearly always is a considerable factor in the production of the disturbance. Of 23 cases of uremia in this hospital studied electrocardiographically, 10 showed gross disturbance of cardiac mechanism, such as intraventricular block, auricular standstill, and so forth, but of these 10, all but 2 had been previously digitalized. The 2 who had not recently received digitalis showed the least marked conduction changes.

One further point of much interest in this case was the extraordinary variations in shape of the ventricular complexes of the electrocardiogram (Figs. 284, A and 285). The position and bizarre appearance of the T wave in Leads I and II are especially notable and quite likely are the result of a toxic effect on intraventricular conduction. Whether the uremic condition alone or the uremia plus digitalization were causes cannot be definitely stated, but it is probable that the uremia was the more important factor.

Case VIII. M. J. E. Rheumatic Heart Disease with Mitral Stenosis and Auricular Flutter Showing Bigeminy from Variation in A-V Conduction.—A married, white housewife of sixty-three, entered the hospital March 10, 1922 for the relief of tachycardia of five weeks' duration.

Present Illness.—For the last year before entrance she had noticed slight dyspnea on exertion. Once about a year and again a few months before entrance she had had attacks of regular tachycardia, lasting about twenty-four hours each. But until five weeks before entrance she had been able to carry on her usual activity without any marked restriction. At this time, however, she had a rather sudden onset of palpitation.

At first it was irregular, but later became regular and remained so. According to her local doctor the rate had not been under 120 since the beginning, and usually averaged 160. At first she carried on her usual activity, but because of increasing dyspnea and weakness she was finally forced to go to bed. She developed a slight cough, with the production of a small amount of frothy sputum. There was no edema or precordial pain at any time. The local doctor gave her various medicines, probably containing digitalis, without result, and sent her to the hospital.

Past History.—At eighteen years of age she had an attack of rheumatic fever. Otherwise the past history was completely negative.

The marital history, family history, social and occupational history, and habits were unimportant.

Physical Examination.—"The patient is a well-developed and nourished elderly woman showing dyspnea and slight orthopnea, but no cyanosis. Aside from the heart condition and a few moist râles at the bases of both lungs the physical examination is negative.

"Heart: The heart shows moderate transverse enlargement, but no increase in the supracardiac dulness. The rate is regular at 150 per minute. The second sound at the apex is loud and ringing."

At entrance no murmurs were made out. Later, with a slower rate, the systolic and middiastolic murmurs of mitral stenosis and regurgitation appeared. Pulse 150.

Urine essentially negative. Renal function = 55 per cent. White blood count = 10,800. Blood-smear not abnormal. Wassermann negative.

Electrocardiogram (Fig. 287, A) the day following entrance showed a tachycardia with rate of 150, consisting of a regular bigeminy, the ventricular complexes of the premature beats being slightly lower in amplitude. The T wave was diphasic.

This presented an unusual picture with some doubt as to diagnosis, between bigeminy from auricular premature beats producing an unusually high ventricular rate, flutter with two to one block, indistinct P waves and varying P-R interval,

and paroxysmal tachycardia, with varying P-R interval. It was expected that further developments would give the answer.

During the afternoon of the day of admission and the next morning she received 0.6 gram of digitalis leaf in divided doses. Then digitalis was omitted as a possible cardiac irritant. The second morning after admission an electrocardiogram (Fig. 287, B) showed a regular tachycardia with a ventricular rate of 155. There was no evidence of bigeminy.

This plate showed the presence of either paroxysmal tachycardia of auricular origin or auricular flutter with two to one

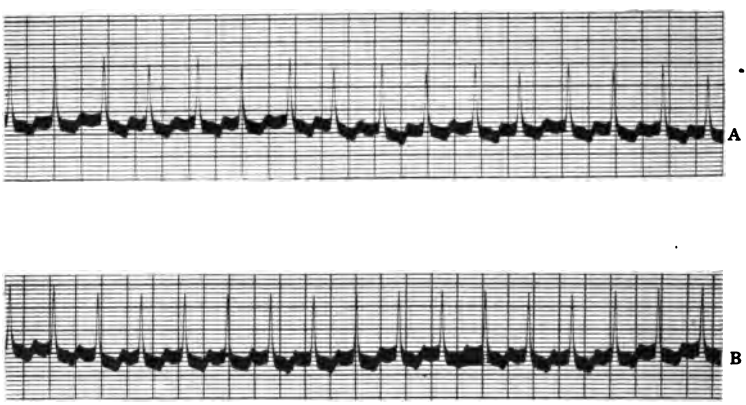


Fig. 287.—Electrocardiogram of M. J. E.: A, Auricular flutter, bigeminy due to variations in the P-R interval, diphasic T wave (Lead II). B, Auricular flutter, auricular rate = 310, ventricular rate = 155 (Lead II).

A-V block, and obscure P waves. The clinical history and course favored flutter; a paroxysmal tachycardia of such duration would be unusual. This regular tachycardia continued without change until March 16th, six days after entrance. On this day digitalis was resumed, 0.1 gram t. i. d. There was no change until the morning of the 19th, when the heart showed variations in rate. Electrocardiograms (Fig. 288, A) from the 19th to the 29th showed definite auricular flutter with A-V block varying from 2 : 1 to 4 : 1. Occasionally the degree of block changed so rapidly that bigeminy appeared. The ventricular rate varied from 82 to 160.

On the 29th the heart became absolutely irregular, and the electrocardiogram (Fig. 288, B) showed auricular fibrillation with a ventricular rate of 80, and a markedly inverted T wave.

Digitalis was stopped in the hope that the fibrillation might spontaneously change to normal rhythm. This, however, did not occur, while she was in the hospital at least. With the slowing of the heart rate there had been much subjective improvement, and she left the hospital April 1st markedly benefited.

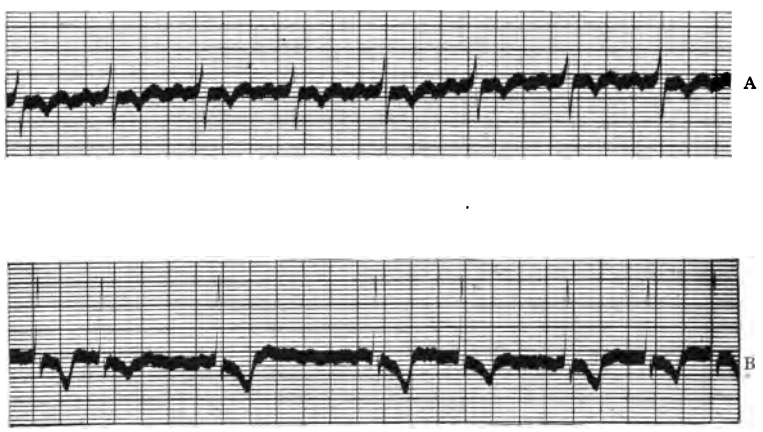


Fig. 288.—Electrocardiogram of M. J. E.: A, Auricular flutter with 4 to 1 A-V block. Inverted T wave (Lead III). B, Auricular fibrillation, inverted T wave (Lead II).

Discussion.—A woman of sixty-three, showing rheumatic heart disease with mitral stenosis and regurgitation, after two short paroxysmal attacks developed a long-continued attack of auricular flutter. During a part of this period there was an unusual bigeminy due to variations in the P-R interval. Opportunity was afforded for studying the transition from flutter to fibrillation.

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